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TEMPERATURE DIFFERENCE IN ORGANS AND TISSUES WITH OBSERVATIONS ON TOTAL OXYGEN UPTAKE IN PROFOUND HYPOTHERMIA

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THE REDUCTION of metabolism effected by lowering temperature has been used for some years to facilitate open heart surgery. The standard method has been external cooling. The more recent introduction of blood stream cooling has greatly widened the scope of hypothermia in the field of cardiac surgery, and much lower temperatures can be obtained safely.

Whatever the method used the organs and tissues do not cool at identical rates. With blood stream cooling, moreover, the pattern of the changes in the temperatures of the organs is quite different from that produced by surface cooling. Since the brain is the organ most quickly damaged by anoxia, it is clearly important that it be possible to estimate its temperature fairly accurately from observations at a more readily accessible site or sites.

The fall in total oxygen consumption during moderate hypothermia produced by external cooling has been well documented, but few figures are available for oxygen uptake under the different conditions and lower temperatures achieved by direct cooling of the blood stream. The present study was devised to provide such information.

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METHOD

Twenty unselected mongrel dogs were perfused by using Drew's technique of left and right heart bypass with autogenous oxygenation, but with a Brown-Harrison heat exchanger in the arterial line (Fig. 1). The coolant was ice water circulated through the heat exchanger at a rate of 25 liters per minute. This sufficed to lower the temperature of the ingoing blood to between 1 and 4 degrees C. When the temperature of the animal had fallen to a predetermined figure, the pump was stopped and complete circulatory arrest maintained for periods of between 5 and 90 minutes. For reheating, water at 40 degrees C. was pumped through the heat exchanger.

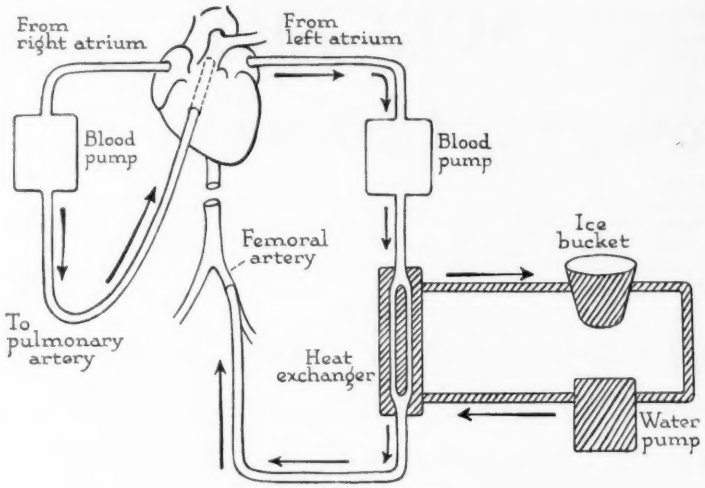

FIG. 1. Extracorporeal circuit.

The extracorporeal circuit was primed with fresh heparinized blood or with a 2 to 1 mixture of blood and dextran.

The dogs were anesthetized with intravenous pentobarbitone and suxamethonium chloride. A close-fitting endotracheal tube was inserted, and respiration was maintained with a Palmer respiratory pump. Oxygen uptakes were calculated from a Benedict-Roth spirometer connected in closed circuit with the respiratory pump.

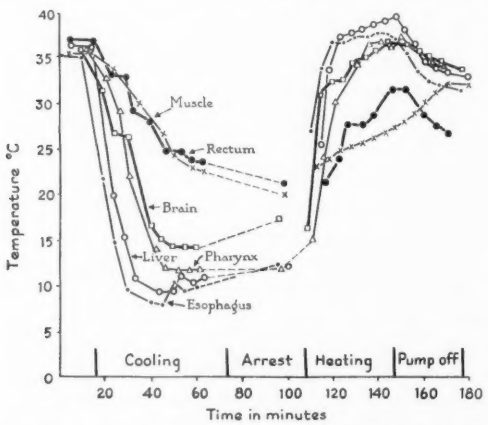

FIG. 2. Dog 10. Temperature differentials during cooling and reheating. The flow rate was 42 cubic centimeters per kilogram per minute.

The dogs respired 100 per cent oxygen throughout the experiment.

The temperatures of selected organs were measured with mercury thermometers and copper-constantan needle thermocouples. Temperatures measured included those of liver, kidney, midesophagus, deltoid muscle, myocardium, parietal lobe of brain, pharynx, and rectum. Total oxygen content of the blood was measured by the manometric method of Van Slyke and Neil, and arterial and venous oxygen saturation was estimated with a Brinkman hemoreflector. Blood samples were collected under paraffin from the right atrium and midabdominal aorta through cannulas inserted via a femoral vein and artery.

RESULTS

The general pattern of the changes in the temperatures of the organs during cooling and rewarming is shown in Figure 2. The midesophageal temperature fell most rapidly. Muscle cooled slowly. The brain temperature followed a middle course. The pharyngeal temperature was often close to that of the brain but not constantly so. The changes in rectal temperature were inconstant. On reheating, the course of events was reversed.

Figure 3 demonstrates that certain organs, viz., heart, liver, kidney and midesophagus cooled rapidly at a comparable rate. The temperature of the blood as it drained from the right atrium bore a close relationship to the temperatures of these organs.

The search for a single accessible organ, the temperature of which bore a constant relationship to that of the brain, was unfruitful but it was noted that the brain temperature consistently fell midway between the midesophageal and muscle temperatures (Fig. 4).

Accordingly, the mean of the temperatures in esophagus and muscle taken at 5 minute intervals during cooling was compared with the brain temperature at these times. Figure 5 shows the composite results obtained in the 11 dogs in which these three temperatures were recorded. An exact correlation between brain temperature and the mean of muscle and esophageal temperatures would cause the points in Figure 5 to lie along the straight line. Most of the readings, especially in the lower temperature range, approximate very closely.

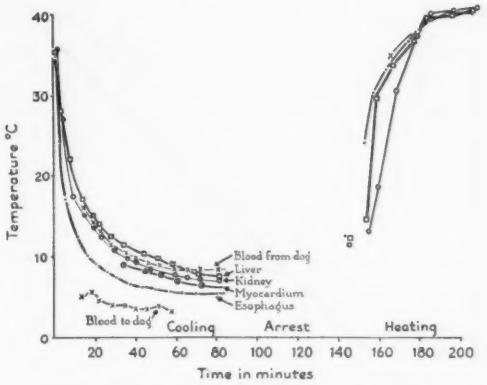

FIG. 3. Dog 17. Temperature differentials during cooling and reheating.

TOTAL BODY OXYGEN UPTAKE

An exponential relationship between the total body oxygen uptake and the muscle temperature was consistently noted. Figure 6 gives an example. The rate of oxygen uptake measured at intervals during cooling and reheating is plotted against the temperature of the deltoid muscle—on a linear scale on the left and a semilogarithmic scale on the right. At a particular muscle temperature the oxygen uptake on reheating was always greater than that observed during cooling. Similar graphs were made in a series of 11 dogs, and the oxygen uptakes at particular muscle temperatures were extracted. In all these dogs the muscle temperature fell below 20 degrees C. and, in 5 dogs, to 15 degrees C. or below. In 6 dogs, the muscle temperature stopped 1 or 2 degrees short of 15 degrees C., and the graphs for these dogs were extended to this temperature. The results are tabulated in Table I. The mean value for total body oxygen uptake at a muscle temperature of 35 degrees C. in the animals was 5.15 cubic centimeters of oxygen per kilogram body weight per minute with a range of 3.7 to 6.8. At 30 degrees C. the total oxygen uptake was reduced to 2.98 cubic centimeters per kilogram per minute—range 2.1 to 4.2—or 58 per cent of the precooling value. At 25 degrees C. a further reduction to 1.75 cubic centimeters per kilogram per minute —range 1.2 to 2.6—or 34 per cent of precooling values and at 20 degrees C. to 1.05 cubic centimeters per kilogram per minute—range 0.65 to 1.6—or 21 per cent of normal was found. At 15 degrees C. the total oxygen

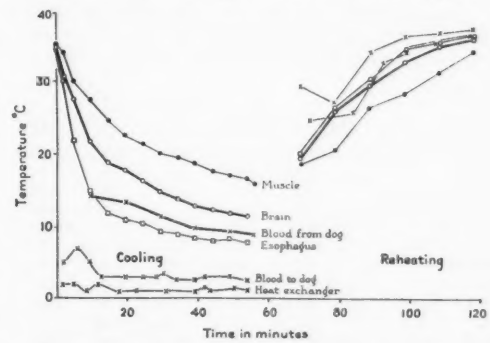

FIG. 4. Dog 16. Temperature differentials during cooling and reheating. Flow rate was 77 to 95 cubic centimeters per kilogram per minute.

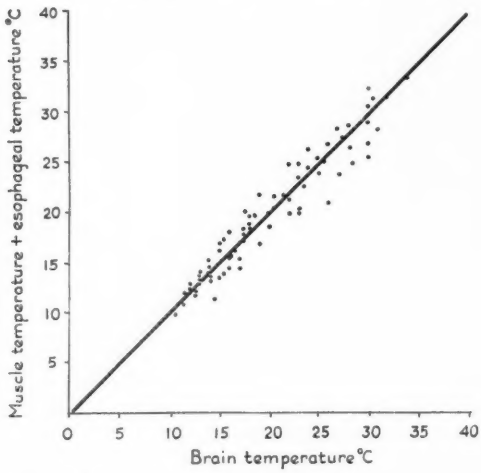

FIG. 5. Mean of muscle and esophageal temperatures graphed against brain temperature. Results taken at 5 minute intervals during cooling from 11 dogs.

uptake was reduced to 0.605 cubic centimeter per kilogram per minute—range 0.25 to 0.9—or 12 per cent of precooling value. The mean values and the range of values obtained are presented graphically in Figure 7.

During the experiments it was noted that at low temperatures there was no apparent arteriovenous difference in oxygen saturation, as measured by the hemoreflector, although spirometry indicated continued utilization of oxygen. Accordingly in the latter part of the series arterial and mixed venous blood samples were withdrawn at low temperatures and analyzed for total oxygen content on a Van Slyke apparatus, the oxygen saturation of the samples being estimated on a Brinkman hemoreflector. The results obtained in the 7 dogs in which these measurements were made are shown in Table II. In dog 12 a negligible arteriovenous difference in oxygen saturation is noted, 0.5 per cent, but there is nevertheless an arteriovenous oxygen difference of 2.2 volumes per cent as measured by the Van Slyke method. In dog 14 at a slightly higher temperature but at a much lower flow rate the oxyhemoglobin dissociates to meet the body's requirements. Dogs 15, 16, and 19 show no appreciable difference in saturation but an appreciable arteriovenous difference in oxygen content. This difference must be in respect of dissolved oxygen. In dog 17 on the other hand, at a very low muscle temperature and a high flow rate, only a minute arteriovenous oxygen difference of 0.2 volume per cent is found.

TABLE I.—TOTAL BODY OXYGEN UPTAKE IN CUBIC CENTIMETERS OF OXYGEN PER KILOGRAM OF BODY WEIGHT PER MINUTE AT VARIOUS MUSCLE TEMPERATURES DURING COOLING IN 11 DOGS

	Muscle temperature, degrees C.				
Dog No.	*35*	*30*	*25*	*20*	*15*
1	3.7	2.1	1.2	0.66	0.38
2	5.4	3.5	2.2	1.4	0.9
3	5.2	2.9	1.65	1.0	0.56
4	4.8	2.8	1.7	1.1	0.66
5	5.2	2.7	1.4	0.7	0.25
6	6.8	4.2	2.6	1.6	0.9
7	5.2	3.5	2.35	1.6	1.05
8	4.4	2.3	1.3	0.75	0.43
9	5.7	3.6	2.25	1.4	0.86
10	5.0	2.6	1.35	0.68	0.36
11	5.1	2.6	1.3	0.65	0.33
Mean	5.15	2.98	1.75	1.05	0.605
Standard deviation	0.76	0.61	0.45	0.37	0.27
Per cent	100	58	34	21	12

DISCUSSION

During blood stream cooling, the temperature of the esophagus falls rapidly, presumably because of its proximity to the cold aorta. The liver, kidney, and myocardium cool almost as rapidly because of their vascularity—under normal conditions the liver and kidney have a blood flow per 100 grams of tissue more than twice that of the brain and many times greater than resting muscle. In our series the temperature of the blood draining from the right atrium followed the temperatures of the liver, kidney, and myocardium fairly accurately. The changes in temperature recorded in the rectum were inconstant, probably because of variation in the degree of loading.

The slow fall in muscle temperature seems likely to be of importance when the circulation is arrested, as the large mass of relatively warm muscle may produce appreciable quantities of lactic acid, thus contributing to a metabolic acidosis. In order to reduce

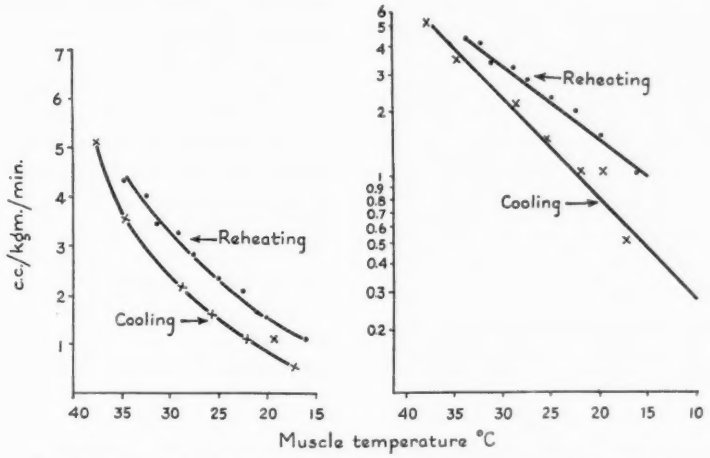

FIG. 6. Dog 11. Total body oxygen uptake graphed against muscle temperature: on a linear scale on the left, a semilogarithmic scale on the right. x--x, Oxygen uptake during cooling. .--., Oxygen uptake during reheating.

the muscle temperature below 15 degrees C. one must either use external cooling in addition to blood stream cooling or prolong the blood stream cooling.

Our studies show that brain temperature is closely related—especially in the lower temperature ranges—to the mean of the temperatures in muscle and midesophagus.

The classical observations of Bigelow on the effect of hypothermia induced by external cooling showed a linear decrease of total body oxygen uptake during cooling and at a rectal temperature of 20 degrees C. an oxygen uptake of 20 per cent of normal—closely comparable to our figure of 21 per cent of normal at a muscle temperature of 20 degrees C. With blood stream cooling, Senning has recorded an oxygen uptake of 0.53 to 0.57 cubic centimeter per kilogram per minute or 10 per cent of normal at a rectal temperature of 19 to 20 degrees C., Young and associates give a figure of 2.60 cubic centimeters per kilogram per minute in children at an esophageal temperature of between 28 and 32 degrees C.—slightly less than 50 per cent of normal—and Gollan and associates 33 per cent of normal at a temperature of 27 to 30 degrees C. Most previous investigators have related total body oxygen uptake to rectal temperature. We have been reluctant to do this because of our dissatisfaction with the validity of the rectal temperatures which were obtained in our experiments. We have chosen to relate total oxygen uptake to deltoid muscle temperature, firstly, because this is easily and reliably measured in both dog and man and, secondly, because the fall in muscle temperature during cooling is slow and steady, unlike that of the esophagus which has a sudden sharp drop at the beginning of perfusion as cold blood fills the thoracic aorta. We have found that the exponential relationship between oxygen uptake and temperature demonstrated by Spurr and associates still holds during blood stream cooling.

TABLE II.—OXYGEN SATURATION AND OXYGEN CONTENT OF ARTERIAL AND MIXED VENOUS BLOOD AT LOW TEMPERATURES

Dog No.	Blood flow, c.c./kgm./min.	O_2 sat., Arterial	per cent Venous	O_2 content, vols. per cent Arterial	O_2 content, vols. per cent Venous	Temperature, degrees C. Muscle	Temperature, degrees C. Esophagus
12	50	95	94.5	17.7	15.5	17.5	7.6
14	30	92	74	17.03	12.1	18.9	12.1
15	35	93	90	13.05	11.5	14.8	9
16	86	90	90	14.6	12.4	16.6	7.4
17	130	96	96	22.9	22.7	8.5	5.7
19	106	96	96	20.35	19.3	25.5	8.5
20	90	98.5	95	17.9	16.9	17.5	5.4

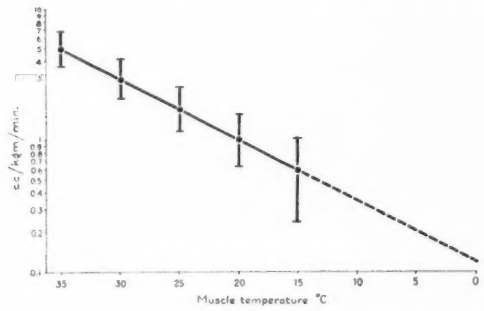

FIG. 7. Graph of mean values of total body oxygen uptake and muscle temperature. •, Mean of total body oxygen uptake during cooling from 11 dogs. I, Range of values obtained.

At a muscle temperature of 25 degrees C. we noted a total oxygen consumption 34 per cent of normal, decreasing to 21 per cent of normal at 20 degrees C. and falling to 12 per cent at 15 degrees C. At these muscle temperatures the "inner core" of body organs is at a very much lower temperature. Figure 2 for example shows that at a muscle temperature of 22 degrees C. the liver temperature is 11 degrees C. It seems possible that at these temperatures a disproportionate amount of oxygen is consumed by the muscles. On the other hand, Fuhrman and others using isolated rat tissues have shown that liver at 10 degrees C. has a higher oxygen consumption than muscle at 20 degrees C. Although in blood stream cooling the over-all body oxygen uptake at a muscle temperature of 20 degrees C. is reduced to 21 per cent of normal, the fall in individual organ oxygen uptake may not be uniform. Thus equal protection from anoxia may not be afforded to all organs.

In measuring oxygen uptake one must ensure adequate oxygenation of the arterial blood. Table II demonstrates that at low temperatures not only is there adequate oxygen available in the arterial blood but also in all the animals, except dog 14, there was sufficient oxygen in solution in the blood to meet the reduced needs of the body. In these animals there is negligible desaturation of oxyhemoglobin but a significant arteriovenous difference in total oxygen content.

It can be argued that the oxygen uptake during hypothermia is reduced because of the inability of oxyhemoglobin to dissociate at low temperatures resulting from the shifting of the oxyhemoglobin dissociation curve to the left. However, we frequently observed that lowering the blood flow rate to minimal levels at low temperatures caused an arteriovenous difference in oxygen saturation to become apparent. This is well demonstrated in Table II in which dog 19 has no dissociation of oxyhemoglobin at a muscle temperature of 25.5 degrees C.—arterial and venous oxygen saturation 96 per cent—whereas dog 14 at a lower muscle temperature, 18.9 degrees C., has an arterial oxygen saturation of 92 per cent but a venous oxygen saturation of only 74 per cent. The reason for this is that the latter animal has a comparatively low blood flow rate of only 30 cubic centimeters per kilogram per minute compared with the flow rate in dog 19 of 106 cubic centimeters per kilogram per minute.

Therefore, the reduction in total body oxygen uptake effected by blood stream cooling is due to a reduction in tissue oxygen demands and not to either a deficiency in the amount of oxygen supplied to the tissues or failure of the hemoglobin to liberate oxygen at these low temperatures.

SUMMARY AND CONCLUSIONS

The temperatures of certain organs and tissues and the total oxygen uptake of the animals at these temperatures were studied in dogs subjected to blood stream cooling.

The temperature of the midesophagus, heart, liver, and kidney fell rapidly and corresponded closely with that of the mixed venous blood in the right atrium.

Muscle cools slowly. Brain temperatures can be estimated reasonably accurately as the mean of the temperatures of muscle and midesophagus.

The total oxygen uptake of the body falls during cooling in an exponential fashion

when recorded against muscle temperature. At a muscle temperature of 15 degrees C. it is reduced to 12 per cent of normal.

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THE POSTOPERATIVE USE OF DEXTRO PANTOTHENYL ALCOHOL

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RECENT REPORTS have suggested that the postoperative administration of dextro pantothenyl alcohol is effective in preventing and in treating enteric atony and ileus. The biochemical basis for using this agent rests upon the work of Lipmann and his associates who in 1950 noted that pantothenic acid forms a part of coenzyme A required for the acetylation of choline to form acetylcholine, the latter being essential to both motor and secretory intestinal activity.

REVIEW

Lynch and his associates have observed significant alterations of tissue pantothenic acid and coenzyme A levels after severe, prolonged, induced, or experimental stress in laboratory animals. More significant, however, is the observation that under the same conditions the intestinal acetylcholine levels were 50 per cent higher at the end of the stress period in those animals which had been protected with dextro pantothenyl alcohol throughout the course of the stress period. Bly and associates demonstrated a 50 per cent loss of intestinal motility in pantothenic acid deficient dogs. Jurgens and Pfaltz observed atony and distention of the gastrointestinal tract in pantothenic acid deficient rats. If pantothenic acid was given before death, the distention disappeared and normal intestinal motility returned.

Dextro pantothenyl alcohol has been administered to several groups of patients during the postoperative course and the findings have been strongly suggestive that this agent was effective in bringing about a more prompt restoration of normal gastrointestinal activity and a shortening of the convalescent period and hospital stay. Haycock and his co-workers, in a double blind study of 100 patients undergoing abdominal operations, found a significant reduction of postoperative nausea and distention with resumption of normal peristalsis after the administration of dextro pantothenyl alcohol. In 112 patients, Frazer and associates found dextro pantothenyl alcohol a safe and effective agent capable of stimulating peristalsis and preventing ileus. Stone and his associates found beneficial intestinal and urinary effects in a series of obstetric patients. Felten gave dextro pantothenyl alcohol to 50 patients with severe postoperative gas pains, constipation, and distention. The majority of the patients expelled flatus within a few hours and there was marked subjective relief.

The early resumption of normal peristalsis after operation not only would seem to be desirable in shortening the patient's discomfort and period of convalescence but also might be of value in increasing the resorption of intraperitoneal fibrin and reducing postoperative adhesions.

METHOD

We desired to evaluate, by means of an objective double blind approach, the efficiency of dextro pantothenyl alcohol in the postoperative management of patients undergoing serious abdominal surgery. The types of procedures studied consisted of resection of aortic aneurysms, gastrecto-

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mies, pancreatectomies, colectomies, portacaval shunts, pelvic peritonitis, transduodenal sphincteroplasties, and operations of similar magnitude. These patients were selected sequentially, at random, according to hospital unit numbers—even numbers to be treated postoperatively with one series of ampules and odd numbers with the other series of ampules, the genuine ampules being indistinguishable from the placebos except by color code. The code was known to only 1 member of the hospital staff who had nothing to do with either the administration of the compound or the selection of the patients. The dextro pantothenyl alcohol or placebo was given in a 2 cubic centimeter dose intramuscularly immediately after operation, again in 2 hours, and then every 6 hours until flatus was passed. The effects were evaluated by the doctors and nurses caring for the patients in terms of hours required to pass flatus and feces, necessity for enemas, and general clinical course; i.e., well being, fever, and distention. Finally, in those cases in which the patients were not kept in the hospital for unrelated reasons, the postoperative hospital stay was calculated in days.

RESULTS

At the completion of the study, 25 patients had received the placebo and 23 had received dextro pantothenyl alcohol. The average age of the patients in the placebo group was 61 years and for the treated group, 64 years. The average duration of the operation was 3.8 and 3.5 hours, respectively. The average time required for passage of flatus by those in the placebo group was 77 hours, whereas it was 69 hours for those in the treated group. The average time for a bowel movement in those patients given the placebo was 116 hours versus 106 hours in the treated group. The average hospital stay was 12 days in the treated as compared to 14 days in the untreated group. In the placebo group it was necessary to administer enemas to 6 of the 25 patients, whereas in the group given dextro pantothenyl alcohol this procedure was necessary in 2 of the 23 patients. No reasonable assay of the effect of dextro pantothenyl alcohol on bladder function could be made because the nature of the procedures was such that an indwelling catheter was required in most patients.

TABLE I.—RESULTS OF FISCHER'S "T" TEST OF SIGNIFICANCE COMPARING PLACEBO AND TREATED GROUPS

Parameters	*Mean difference*	*"t" values*	*"p" values*
Flatus	531	4.886	0.0002
Feces	741	4.315	0.0002
Hospital stay	71	3.794	0.0002

A significant difference is present when $p<0.05$.

At the conclusion of the study it was thought that 3 observed parameters lent themselves to statistical analysis: (1) hours required for passage of flatus; (2) hours required for passage of feces, and (3) duration of the postoperative hospital stay.

Fischer's "t" test of significance was used to match the group of patients who received the actual drug against those of the placebo group. The results indicated that the drug had a significant effect in all 3 of these parameters (Table I). As can be seen from the tabulation, these findings are of statistical significance with a "p" value of .0002 in each case indicating that these findings would occur by chance less than 2 times in 10,000 trials.

It must be recognized that these values while high in statistical significance are based upon very subjective figures. Nevertheless, the findings suggest that the administered dextro pantothenyl alcohol produced a statistically significant difference in these groups.

There was a distinct difference in the grading of the postoperative clinical course based on an over-all subjective evaluation by the resident and nursing staffs. Thirteen of 23 or 57 per cent of the dextro pantothenyl alcohol treated patients rated an excellent postoperative course as compared with only 8 of 25 or 32 per cent with this rating in the placebo group.

There were no reactions or untoward effects attributable to the administration of dextro pantothenyl alcohol in this series of patients.

CONCLUSIONS

In this double blind study of 48 older patients undergoing abdominal surgery the postoperative administration of dextro pantothenyl alcohol resulted in a significantly earlier restoration of the patients' intestinal activity.

Patients in the treated group were discharged from the hospital an average of 2 days earlier than were those in the control group.

Dextro pantothenyl alcohol would seem to be a safe and effective agent of value in the management of postoperative ileus and distention.

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INTESTINAL GANGRENE ASSOCIATED WITH HEART DISEASE

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THE PRINCIPLE that massive bowel infarction is the result of superior mesenteric artery or vein occlusion is universally accepted. Occasionally, however, no vascular occlusion is found at postmortem examination, and the absence of the anticipated block is conveniently attributed to the inexperience or negligence of the prosector. This unsatisfactory explanation prompted us to review the records of patients with massive bowel infarction at the Boston City Hospital and the Mallory Institute of Pathology.

MATERIALS AND METHODS

During the 12 year period between 1945 and 1956 autopsy was performed in 110 cases of massive bowel infarction. Gangrene caused by mechanical disturbances such as volvulus, hernia, or intestinal obstruction was not included in this study. In 87 instances the mesenteric vessels contained one or more major blocks while in 23 cases no occlusions could be demonstrated. Only cases in which the prosector specifically stated that dissection of the mesenteric arterial and venous trees was performed were accepted into the latter group of nonocclusive infarctions. The clinical records of these 23 patients were then analyzed.

RESULTS

There were 13 males and 10 females. The average age was 69 years, the range 50 to 91 years, with the average male dying of this disease 10 years before his female counterpart.

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Massive nonocclusive infarction of the bowel was an acute, rapidly progressing, and fatal disease. Abdominal pain with shock was the most constant and striking feature. Most commonly the abdominal pain was severe and relentless but an occasional patient complained of crampy pain. Its localization varied from generalized abdominal pain to pain in any of the four quadrants.

The physical findings were equally diverse. In 11 patients no striking abdominal signs were noted. The others manifested diffuse or localized lower abdominal tenderness with or without spasm. Distention was present in 6 instances. Bowel sounds ranged from absent to hyperactive. Since the combination of signs and symptoms did not follow any uniform pattern and because of the frequency of the associated heart disease, the abdominal findings were minimized by the clinicians. The diagnosis of bowel infarction was entertained only in the 6 patients with abdominal distention.

Four patients had had previous hospital admissions for similar illnesses, while 12 had histories of premonitory gastrointestinal disturbances lasting from weeks to months. Intermittent abdominal pain, frequently in association with meals, was the most common symptom followed by anorexia, weight loss, and diarrhea in that order.

One patient had concurrent massive pulmonary embolization while 3 others had acute myocardial infarctions. Twenty-four hours before death, and 24 hours after the appearance of abdominal pain, symmetric gangrene of the lower extremities developed in a 63 year old man. Autopsy revealed

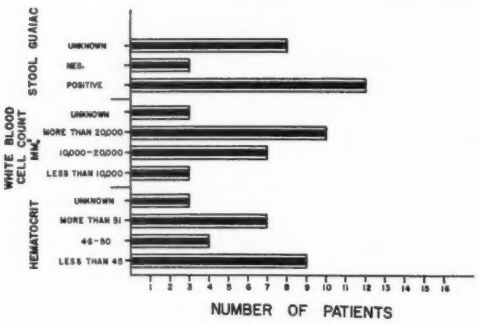

FIG. 1. Laboratory data.

patent vessels supplying the involved limbs.

Decompensated heart disease was definitely present in 21 patients and questionably so in the remaining 2. In 17 cases the clinical impression of congestive heart failure was confirmed by autopsy. In the other 4 it was first recognized during postmortem examination. The autopsy findings in the 2 doubtful cases were suggestive but not conclusive of decompensated heart disease. The degree of congestive failure was variable and, therefore, no correlation could be established between the severity of the heart disease and the occurrence of nonocclusive or functional infarction. The latter two terms will be used interchangeably in this article. The type of the heart disease, the cardiac rhythm, and the blood pressure did not appear to have any etiologic significance either. It is interesting to note, however, that with the clinical diagnosis of auricular fibrillation, the prosector usually attributed the infarction to mesenteric embolization even in the absence of a demonstrable embolus.

The laboratory findings were similar to those seen in mesenteric thrombosis, i.e., leukocytosis, elevated hematocrit, and guaiac positive stool (Fig. 1). Three patients had consistently positive stools associated with abdominal pain for the 3 week period immediately preceding the acute illness. Postmortem examinations failed to establish any cause other than the infarction for the gastrointestinal bleeding.

The duration of shock was short in most instances (Fig. 2). Vasopressor drugs (levophed and neosynephrine) were given to 3 patients, and 1 was receiving dicumarol therapy at the time the infarction occurred. Those who were given more than a single dose of antibiotics lived an average of 7.5 days after the onset of their symptoms while with a single dose or no antibiotics, the average survival time was 3.2 days.

On postmortem examination, there was a moderate variation in the extent of the gangrenous process. Infarction in the distribution of the superior mesenteric artery was by far the most common pattern followed by involvement of multiple segments of the small and large bowels at random sites. The third and least frequent finding was infarction of the entire large and small bowels (Fig. 3).

The following is an illustrative case history of a patient with several hospital admissions.

A 62 year old, white watchman entered a Boston hospital in June 1947 with a 4 month history of progressive weakness, exertional dyspnea, and intermittent left-sided chest pain. Two weeks prior to admission the patient experienced an episode of severe squeezing precordial pain and associated with this he noted, for the first time, a similar pain in the upper part of the abdomen. On the morning of admission both the chest and abdominal pains recurred and shortly thereafter he had a bloody bowel movement. Family, social, and past histories were noncontributory. Review of the systems revealed

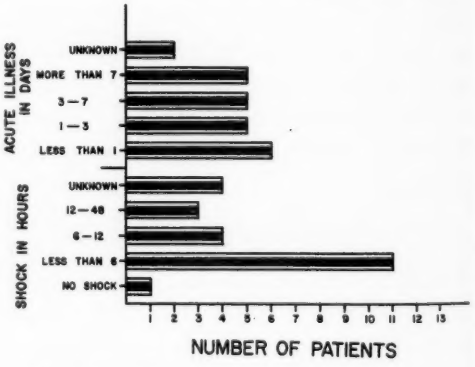

FIG. 2. Duration of shock and length of the acute terminal illness.

that he had been a healthy man until the onset of the presenting illness.

On admission, the patient was in acute respiratory distress and complained of precordial and severe left-sided abdominal pains. The neck veins were distended, the heart was enlarged to the left, and it was galloping. Rales were heard at both lung bases. The abdomen was slightly distended and diffusely tender. There was moderate pretibial edema.

The initial diagnostic impression was myocardial infarction with congestive heart failure, and the possibility of a dissecting aneurysm was raised.

Rapid digitalization was started soon after admission and dicumarol was given for 3 days. Within 48 hours the cardiac function improved and the abdominal pain subsided. After 25 days in the hospital the symptoms abated and the patient was allowed to return to his home.

For 5 months the patient did well, but then the dyspnea and abdominal pain recurred. He was admitted to the hospital in marked congestive failure. The abdomen was diffusely tender with spasm in the right lower quadrant. Digitalis was continued and intensive diuretic therapy was instituted. There were frequent bouts of crampy abdominal pain in the hospital. The bowel movements were frequent and loose. A barium enema revealed a normal colon. Within 2 weeks the cardiac failure had cleared, the abdominal pain disappeared, and the patient was discharged.

During the ensuing 9 months the patient did well. Then he became ill again. This time crampy abdominal pains and nausea were the presenting symptoms. They were accompanied by palpitation and chest pain. Dyspnea was also present. Physical findings were similar to those on previous admissions except for a grossly irregular heart rhythm and more impressive abdominal signs. There was diffuse abdominal tenderness with spasm and rebound tenderness in the left lower quadrant. Mesenteric thrombosis was listed, for the first time, among the diagnostic possibilities. Intensification of the cardiac regimen resulted again in marked improvement of all symptoms and signs.

Three weeks after discharge, on 1 October 1948, the patient entered the Boston City Hospital with a 2 week history of dyspnea and abdominal pain, radiating to the left side of the chest. The pain was frequently followed by vomiting. He was in marked congestive failure. The abdomen was slightly distended with spasm and tenderness most marked in the left lower quadrant. The temperature was 103 degrees F., the white blood count 15,000, and the stool guaiac positive. An abdominal catastrophe (? mesenteric thrombosis) was believed to be the primary problem. In view of the patient's poor cardiac function, the surgical consultant recommended conservative therapy. The cardiac regimen was again intensified but this time the patient failed to rally. Bloody diarrhea developed and narcotics were required for the relief of the abdominal pain. The patient grew weaker and finally expired on the twenty-first hospital day. Autopsy revealed patchy infarction of the small and large bowels in the distribution of the superior mesenteric artery. The superior mesenteric artery as well as the vein and all their major branches were examined. They were found to be elastic and patent. In addition, the clinical impression of arteriosclerotic heart disease was confirmed by the autopsy. The lungs were congested and there was pleural effusion on the right side.

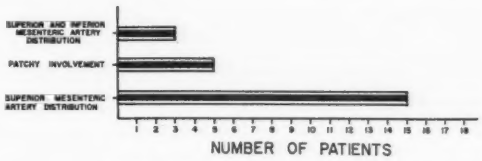
SUPERIOR AND INFERIOR MESENTERIC ARTERY DISTRIBUTION
PATCHY INVOLVEMENT
SUPERIOR MESENTERIC ARTERY DISTRIBUTION
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17 18
NUMBER OF PATIENTS

FIG. 3. Extent of bowel infarction.

DISCUSSION

The data presented in this article and other reports in the literature suggest that nonocclusive bowel infarction is a real clinical entity. Ende described 3 cases of massive bowel infarction without occlusion and discussed 3 more with less severe involvement of the bowel. Glotzer and Shaw, in assessing the potentialities of reconstructive vascular surgery in 31 patients with massive bowel infarction, found that 9 of them were ineligible for surgical treatment because of the absence of demonstrable occlusions. As far as the so called "unexplained" infarctions are concerned, a case report from the Massachusetts General Hospital (2) demonstrates poignantly that it is a slim explanation to accuse the prosector with negligence for his failure to find the occlusive clot in these cases. The pathologist, faced with a case of suspected mesenteric thrombosis and having had meager fortunes in locating the thrombus on a similar occasion in the past, summoned 2 surgeons to witness the autopsy. The bowel was obviously infarcted but the mesenteric arterial and venous trees contained no clots in spite of a thorough search by all 3 present.

In a search for a common denominator in these cases we found the frequent co-

existence of congestive heart failure striking. It was definitely present in over 90 per cent of our cases and in all of Ende's 6 patients. Glotzer reported the clinical and not the autopsy evidence of associated congestive heart failure. Still the incidence was 67 per cent in the nonocclusive group and only 23 per cent in the thromboembolic group. Such a frequent combination of these two diseases would indicate that congestive heart failure is an etiologically significant background disease in functional bowel infarction.

In congestive heart failure compensatory vasoconstriction redistributes available effective blood supply from the skin, muscles, and splanchnic bed to the more vital organs such as heart and brain. The existence of a powerful vasoconstrictor apparatus in the splanchnic bed has been demonstrated both in man and animals. With sudden embolic occlusion of the superior mesenteric artery, vessels distal to the site of occlusion undergo severe spasm and in fact blood flow may not resume for some time after embolectomy. Furthermore, there are cases of nonocclusive infarction on record in which at laparotomy the injection of novocain into the root of the mesentery or percutaneous splanchnic block resulted in return of viability to the ischemic bowel. This change was presumably achieved by novocain induced relaxation of spastic vessels. In dogs, repeated injections of epinephrine produces ischemic bowel lesions. Laufman and Method, working on dogs, concluded that vasoconstriction plus contraction of the mural musculature of the bowel are powerful enough to cause frank gangrene. It seems that in congestive heart failure the compensatory vasoconstriction in the splanchnic bed may occasionally be severe enough to cause ischemia of the bowel. Reacting to the ischemia secondary mural muscle spasm further reduces effective blood supply. Once this vicious cycle is set into motion intestinal bacteria begin to thrive and the full blown picture of gangrene with toxemia appears on the scene.

It is interesting to note here that cardiogenic gangrene can occur in the lower extremities. One of our patients was found to have extensive gangrenous changes in both legs without any evidence of obstructing lesions in the pertinent vessels on postmortem examination. Similar events have been reported by Cotton and Bedford and by Abrahams.

From a theoretic point of view, any type of vascular collapse with the accompanying compensatory splanchnic vasospasm may precipitate functional bowel infarction. Animals subjected to irreversible shock by any of the standardized methods show diffuse necrosis and sloughing of their gastrointestinal tracts. Irreversibility is attributed to absorption of toxins and free hemoglobin by the injured bowel. However, bowel necrosis is not a well substantiated lesion in human shock. Moreover, in the majority of our cases it was possible to establish that the abdominal pain preceded shock. Certainly it is possible that the shock produced by the ischemic bowel added further insult to an already injured organ, thereby contributing to a state of irreversibility.

The treatment of nonocclusive bowel infarction is far from satisfactory, yet recognition of this entity and the correct diagnosis is of primary importance. This point is emphasized only because of the extremely low index of suspicion demonstrated by our clinicians. The appearance of abdominal pain in the presence of congestive heart failure heralds grave consequences and warrants careful appraisal. The clinical picture and the laboratory findings have already been alluded to. A simple roentgenogram of the abdomen may show dilated small and large bowel patterns with absence of air beyond the midtransverse colon. Abdominal tap is another helpful diagnostic tool. In 18 of the 23 cases the peritoneal cavity contained ample bloody fluid to produce positive taps.

Once the diagnosis of ischemia of the bowel is entertained all available therapeutic measures should be immediately

mobilized. Vigorous treatment of the cardiac failure may in itself reverse early infarction. Antibiotics are known to prolong bowel survival by reducing the bacterial population and toxin production. Intestinal intubation eliminates circulatory embarrassment secondary to bowel distention. Vasopressor agents should be used cautiously, for, in addition to maintaining normotensive levels, they may reduce mesenteric blood flow and thereby potentiate the original pathologic process. Several investigators have shown that in experimental endotoxin shock sympathomimetic drugs increase mortality rates and sympatholytic agents provide partial protection from irreversible shock.

If the abdominal pain fails to abate and the signs progress, emergency laparotomy, if at all feasible, is indicated. The surgical approach to thrombosis or embolism of the superior mesenteric artery is fairly well established. The nonocclusive variety of the disease presents a more challenging and essentially a novel surgical problem. According to several reports, promising results have been attained by the injection of novocain into the root of the mesentery, and, therefore, this procedure deserves serious consideration in the treatment of functional infarction of the bowel.

SUMMARY

Twenty-three cases of nonocclusive massive bowel infarctions are presented. Coexisting congestive heart failure was found in over 90 per cent of the patients, and therefore it is believed that decompensated heart disease is a major causative factor. It is proposed that the mechanism of the infarction is compensatory vasospasm in the splanchnic bed.

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HISTOCHEMICAL OBSERVATIONS ON THE POLYP-CARCINOMA SEQUENCE

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THE IDEA that adenomatous polyps of the colon represent precancerous lesions has developed as a result of several observations. Clinicians have noted the frequent association of polyps and carcinoma in the same individuals, the close parallelism in distribution of the two lesions with respect to sex, race, and location in the colon, the peak age incidence occurring 5 to 10 years earlier among patients with polyps, and the rather constant appearance of carcinoma in patients with familial polyposis whose colons are not resected. These clinical data are supported by the frequent findings in polyps of histologic alterations extending from simple cellular atypism to frank invasive carcinoma. On the other hand, the benign course which most polyps follow, the rare documentation of benign polyps undergoing malignant change even during long observation periods, and the difficulties associated with microscopic classification have led some to question the validity of the circumstantial evidence given. The details of the arguments for and against the concept that polyps are potentially malignant lesions have been reviewed adequately by several investigators.

The discordant views expressed by both clinicians and pathologists served to emphasize that more information was needed. Although the biochemical aberrations that result in the transformation of a normal cell into a malignant one are not known, certain differences have been recognized. For example, it has been noted that various enzymatic activities are often decreased in malignant cells, as compared with the normal cell of origin. This observation suggested that a study of various enzymatic activities in normal colon mucosa, adenomatous polyps, and colon carcinoma might furnish some biochemical evidence concerning this issue. If polyps were indeed premalignant lesions, one might expect that changes from the normal to the carcinoma should be reflected in the polyps.

When this study was begun, biochemical data on this subject were sparse. However, since then Wattenberg (9, 10) has published his studies on the histochemical localization of several oxidative enzymes in proliferative lesions of the colon; while Cole and McKalen and Stich and associates have reported on nuclear desoxyribose nucleic acid in cells of normal colon mucosa, adenomatous polyps, and adenocarcinomas. These studies as well as our own fail to offer significant biochemical evidence either to support or to refute the concept that polyps are premalignant lesions.

MATERIALS AND METHODS

Tissue preparation. The material studied included 17 normal colons, 43 adenomatous polyps, 7 carcinomas in situ, and 13 adenocarcinomas, all from different patients. Fresh specimens were obtained from the operating rooms or from the autopsy room when the examination was performed within 6 hours after death. The material from each source was about equally divided. Although the surgical tissues showed less surface autolysis, differences in enzymic preservation were not significant. The polyps were cut through the stalk and adjacent base. Occasionally large pedunculated polyps had

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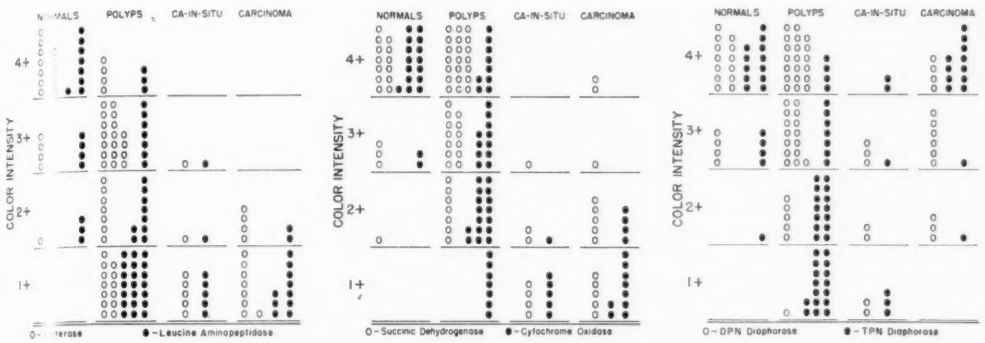

FIG. 1. The significance of the 1+ to 4+ grading of color intensity is described in the text. Each circle represents 1 specimen. Despite the variations among the individual specimens, the pattern that becomes apparent is a marked decrease in enzymatic activities of esterase and leucine aminopeptidase and a moderate decrease of succinic dehydrogenase and cytochrome oxidase in the abnormal epithelial cells of the polyps and carcinomas as compared to the normal colonic mucosa. While the diaphorases are decreased similarily in the polyps, the malignant lesions show activities equal to or greater than that seen in the normal epithelium. This is most striking for TPN diaphorase.

to be cut into several blocks. Carcinomas were trimmed to include the margin of the tumor and the adjacent normal mucosa. The samples of normal colon were obtained largely at the time of necropsy. Small blocks were cut and frozen rapidly by immersion in isopentane, previously cooled to about −70 degrees C. in a dry ice and acetone bath.

Histochemical methods. Ten or more serial 12 micron sections were cut in the cryostat. The first and last sections were stained with hematoxylin and eosin. The others were incubated in various media (2-7) designed for the histochemical demonstration of cytochrome oxidase, succinic dehydrogenase, diphosphopyridine nucleotide (DPN) and triphosphopyridine nucleotide (TPN) diaphorases, esterase, and leucine aminopeptidase. These enzymes were chosen for study because they are active in normal colonic mucosa, because reliable methods are available for their demonstration, and because they represent examples of some of the enzymes concerned with the respiratory, proteolytic, and hydrolytic activities of cells. The duration of the incubation periods were kept constant for each enzyme—cytochrome oxidase, 60 minutes; succinic dehydrogenase, DPN and TPN diaphorases, and esterase, 15 minutes; and leucine aminopeptidase 120 minutes.

The grading of enzymatic activity was done by both gross and microscopic viewing with a scanning lens (×20). The following scheme was adopted: grade 1 indicates no pigment or occasional granules; grade 2 means a weak but definite stain; grade 3 equals moderate staining; and grade 4 sections show a strongly positive reaction. This semiquantitative means of estimating enzymatic activity is accurate to the extent that measured amounts of pigment in multiples of four when placed upon sections can be identified readily as more or less than a known control slide. In a number of specimens, the grading was done separately by each of us and close correlation was observed.

Pathologic classification. The polyps studied were only of the adenomatous type, since no villous adenomas were encountered. They were composed of two distinct epithelial cell types, the goblet cells which produced mucus, and other nonsecretory cells resembling the superficial colonic mucosal cells. In most instances one or the other of these cell types predominated, but occasionally the polyps contained almost equal numbers of goblet and nonsecretory cells.

FIG. 2. Low power magnification of an adenomatous polyp stained with hematoxylin and eosin, ×5. The arrow points to the junction of normal and polypoid epithelium which is shown in the enzyme stains which follow.

The criteria for the diagnosis of carcinoma in situ vary in different institutions. This designation was used in our cases for lesions which showed disorganized cell populations, hyperchromatism, lack of acini formation, and abnormal nuclei and mitoses, that is, lesions with all the cytologic characteristics of malignancy except for invasion into the submucosa. Among the adenocarcinomas there were 4 very invasive, poorly differentiated growths and 3 mucus-producing tumors.

RESULTS

Normal mucosa. Although several of the enzymes were active in the muscularis and other components of the colon, the observations will be confined to the cells in the mucosa. In most instances the activities of succinic dehydrogenase, DPN and TPN diaphorases, and cytochrome oxidase were fairly uniform throughout the depth of the mucosa. This is not readily apparent at first glance but is observed when the pigment deposition in the cytoplasm of the various cells is compared. The surface cells and, sometimes, cells in the depths of the crypts which appear to be more heavily stained than others actually contain more cytoplasm and little or no mucus. When the mucus areas are ignored, the cytoplasm of the goblet cells distributed throughout the crypt is equally active. We could not confirm the observation of Wattenberg (10) that the oxidative enzymes were less active in the mid-region of the crypts than at either end. However, with esterase and leucine aminopeptidase, a real increase in activities is noted from the deeper to the more superficial cells of mucosa. Another difference noted with the latter enzymes was the high activity in the luminal portions of cells, especially those of the surface epithelium.

The activities of the enzymes studied showed only slight variations among the 17 specimens of normal mucosa. Most revealed an abundant deposition of pigment and were graded as 4+; approximately one-quarter were graded 3+. Representative examples of the staining reactions in normal colonic mucosa may be seen in the photomicrographs containing both polyps and carcinoma. The variations seen among the specimens studied are illustrated by the scattergrams.

Adenomatous polyps. The activities of the normal mucosa adjacent to the stalks of the polyps were more variable than in normal mucosa unassociated with polyps. In general, the enzymes were less active in the normal cells nearby, when they were also less active in the polyp. As can be seen in the scattergrams (Fig. 1), many polyps showed enzymatic activities graded 4+ and 3+, comparable to the controls. However, there were significant numbers of polyps with weak or no staining (2+ and 1+). Succinic dehydrogenase and DPN diaphorase appeared to be least depressed among the polyps in our study. Occasionally, succinic dehydrogenase was slightly more active in the polyp. Otherwise, the fall off in activities in the polyps were most marked for leucine aminopeptidase, esterase, TPN diaphorase, and cytochrome oxidase. Indeed, while normal mucosa showed a weak stain only occasionally, such low activities (2+ or 1+) were observed in the polyps at rates of 75 per cent for leucine aminopeptidase, 73

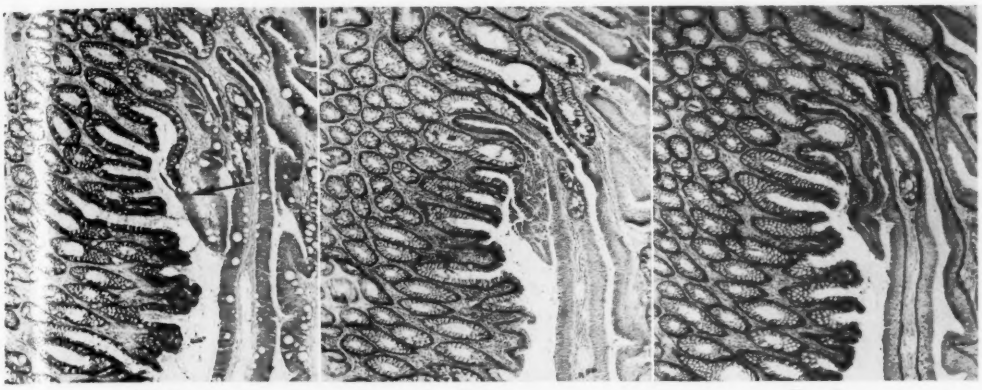

FIG. 3. FIG. 4. FIG. 5.

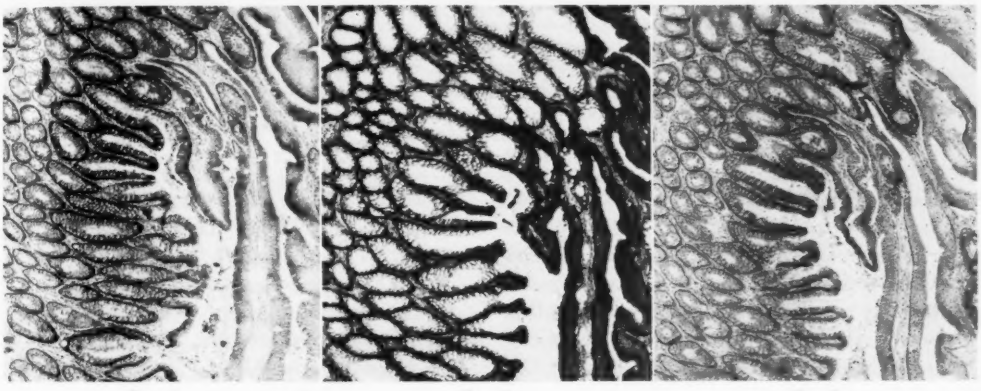

FIG. 6. FIG. 7. FIG. 8.

FIGS. 3 to 8. Higher magnification, ×19, of the same polyp showing various enzymatic activities in the normal and polypoid epithelium. The arrow in Figure 3 focuses attention on the change in the surface epithelium. In each instance, except for Figure 7, there is a marked decrease in enzymatic activity at this site. These observations are much more striking in the original slides in which enzymatic activity is shown by colored pigments. In these photomicrographs the gray color does not represent weaker sites of enzymatic activity but is due mostly to refraction of light or background stain of diazonium salts. Activities are shown for: esterase (Fig. 3); leucine aminopeptidase (Fig. 4); cytochrome oxidase (Fig. 5); succinic dehydrogenase (Fig. 6); DPN diaphorase (Fig. 7); TPN diaphorase (Fig. 8).

per cent for TPN diaphorase, 53 per cent for cytochrome oxidase, 48 per cent for esterase, 17 per cent for succinic dehydrogenase, and 15 per cent for DPN diaphorase. The decrease in enzymatic activity in a given polyp does not necessarily apply to all of these enzymes studied. Thus, in 1 instance succinic dehydrogenase and DPN diaphorase may be graded 4+; TPN diaphorase and cytochrome oxidase 2+; and leucine aminopeptidase and esterase, only 1+. In another polyp, an entirely different pattern may be seen, such as a reduction in only 2 of the 6 enzymes. Aside from a general depletion in more than 1 enzyme, no definite pattern could be seen. A fairly characteristic reaction pattern is shown in Figures 2 to 8 in which the normal mucosa was positive for all 6 enzymes, as shown in the left half of each figure, and the epithelium of the polyp demonstrated a marked reduction of all but DPN diaphorase (Fig. 7).

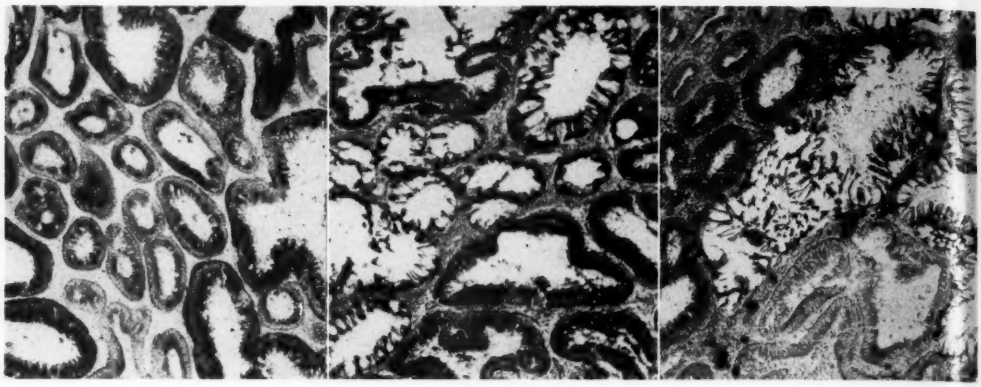

FIG. 9. FIG. 10. FIG. 11.

FIGS. 9 to 11. These sections through an adenomatous polyp illustrate some of the variations seen in enzymatic reactivity. The goblet cells which contain less cytoplasm appear to have less enzyme. Although it may not be clearly visible in all 3 figures at this magnification, ×60, Figure 11 shows the rather frequent finding of decreased enzymatic activity in the atypical cells and disorganized acini in the lower portion of the figure, in contrast to the abundant enzymatic activity in more normal appearing glands in the left upper portion of figure. Reactivities are shown for: succinic dehydrogenase (Fig. 9); DPN diaphorase (Fig. 10); cytochrome oxidase (Fig. 11).

Besides this general phenomenon of decreased enzymatic activities, other differences were noted in the polyps. Rather striking variation was seen in the intensity of staining in different portions of the polyp, especially those with several degrees of cellular atypism (Figs. 9 to 11). When the acini were less perfectly arranged, and the cells appeared to be more proliferative, succinic dehydrogenase (Fig. 9), DPN diaphorase (Fig. 10) and cytochrome oxidase (Fig. 11) were less active.

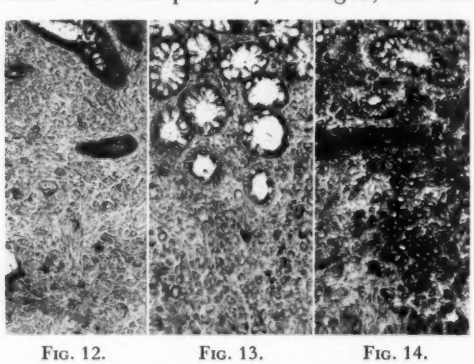

FIG. 12. FIG. 13. FIG. 14.

FIGS. 12 to 14. These sections are from a small focus of anaplastic carcinoma in situ along the stalk of an adenomatous polyp. In the upper portion of each photomicrograph, ×68, a few benign acini are visible for comparison. While succinic dehydrogenase (Fig. 12) and cytochrome oxidase (Fig. 13) are much less active in the neoplastic than in the normal cells, the reverse is true for TPN diaphorase (Fig. 14).

Carcinoma in situ. The 7 specimens which were designated carcinoma in situ had all the cytologic characteristics of malignancy except invasiveness. It was interesting to observe that those areas in the polyps which looked histologically benign had the enzyme reaction pattern described, while the sites showing loss of cellular organization, piling up of nuclei, and loss of nuclear polarity resembled the enzymatic pattern of the carcinomas; namely, a striking decrease in cytochrome oxidase, esterase, leucine aminopeptidase, and succinic dehydrogenase, but a strong or even increased reaction of DPN and TPN diaphorases. Similar findings with reference to the oxidative enzymes were noted in the 3 malignant polyps reported by Wattenberg (9). Our only disagreement is with his statement that increased DPN diaphorase activity was more widespread than that of TPN diaphorase. Our findings showed little difference; if anything, TPN diaphorase was more active. Figures 12 to 18

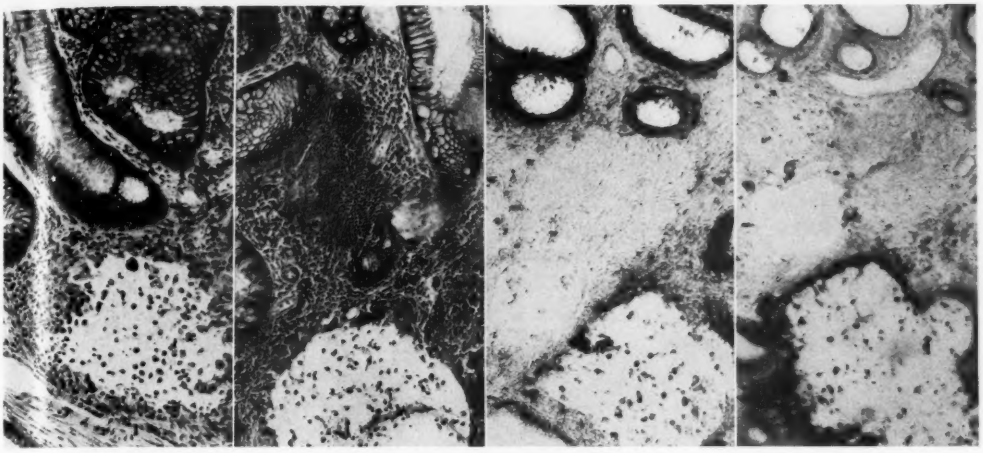

FIG. 15. FIG. 16. FIG. 17. FIG. 18.

FIGS. 15 to 18. These figures demonstrate a small focus of mucinous carcinoma in situ in the tip of an adenomatous polyp. The neoplastic cells are best seen in this section stained with hematoxylin and eosin (Fig. 15). In Figure 16 these abnormal cells appear to contain leucine aminopeptidase, but the dark gray color is actually nonenzymatic background stain. The absence of this background gives a truer picture as is seen in Figure 17 where the reaction for cytochrome oxidase is strongly positive in the normal acini above and negative in the abnormal mucinous cells. However, these cells are strongly reactive for TPN diaphorase (Fig. 18). All views were taken at a magnification of ×86.

show the reactions of several enzymes in the normal acini of 2 polyps, shown in the upper portions of the photomicrographs, and in the 2 small foci of carcinoma in situ within these polyps. In the first polyp, succinic dehydrogenase (Fig. 12) and cytochrome oxidase (Fig. 13) activities are strikingly decreased in the abnormal cells, while TPN diaphorase (Fig. 14) was more pronounced in the neoplastic cells. In the second polyp the mucinous characteristic of the carcinoma in situ focus set it apart from the remainder of the polyp, as may be seen in the section stained with hematoxylin and eosin (Fig. 15). The malignant appearing cells in the mucin contain very little leucine aminopeptidase (Fig. 16) and cytochrome oxidase (Fig. 17) but are strongly reactive for TPN diaphorase (Fig. 18). More often the routinely stained section showed much less contrast than those stained for enzymatic activities in which there was either an almost complete absence of pigment in the focus of carcinoma in situ (cytochrome oxidase, succinic dehydrogenase, leucine aminopeptidase, or esterase), or else increased pigment deposition in the malignant area (DPN or TPN diaphorase activities).

Carcinoma. In nearly every instance the normal epithelium adjacent to a carcinoma contained enzymatic activities similar to that seen in other normal colonic mucosa. As mentioned previously, the usual reaction seen in the malignant epithelium was a marked decrease in the activities of cytochrome oxidase, succinic dehydrogenase, leucine aminopeptidase, and esterase, but normal or even increased activities of DPN and TPN diaphorases. These results and the variations among the specimens may be seen in the scattergrams. Thus, the activities were in the abnormal ranges (1+ to 2+) in all of the cases with reference to esterase, leucine aminopeptidase, and cytochrome oxidase, and in 10 of 13 instances for succinic dehydrogenase. However, only 3 and 1 of the 13 specimens showed decreased activities for DPN and TPN diaphorases,

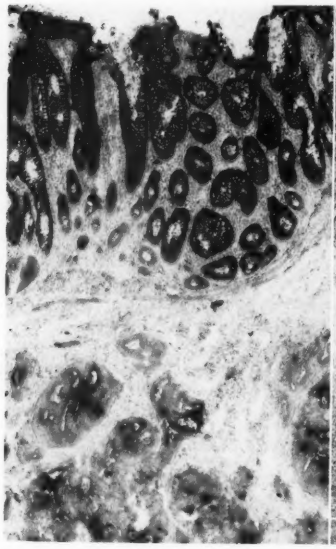

FIG. 19.

FIG. 20.

FIG. 21.

FIG. 22.

FIG. 23.

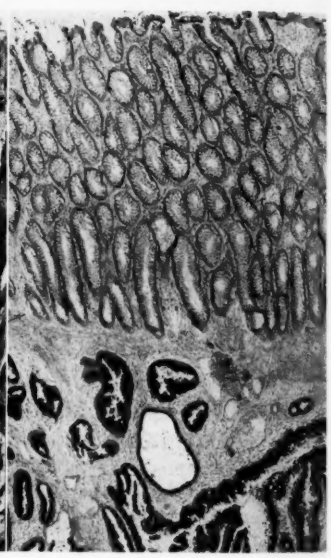

FIG. 24.

FIGS. 19 to 24. These sections were cut from the periphery of an adenocarcinoma and illustrate the enzymatic reactions in the normal mucosa above and in the carcinomatous infiltrate in the submucosa. This is a fairly typical pattern showing reduction in activities in the carcinoma, of esterase (Fig. 19), leucine aminopeptidase (Fig. 20), cytochrome oxidase (Fig. 21), and succinic dehydrogenase (Fig. 22). What appears to be leucine aminopeptidase activity in the submucosal tumor (Fig. 20) is actually enzymatic activity in the fibroblasts which are encasing the weakly reactive malignant epithelial cells. The many deposits of pigment in the submucosa which are seen in Figure 21 represent white blood cells with strong peroxidase activity. In contrast to these figures, DPN diaphorase activity in the carcinoma (Fig. 23) is equal to that seen in the normal epithelium, while TPN diaphorase (Fig. 24) is much more active in the malignant than in the normal cells, ×28.

respectively. Indeed, the scattergrams do not show that DPN and TPN diaphorases were often more active in the carcinoma. The photomicrographs emphasize this feature more satisfactorily, as may be seen in Figures 19 to 24.

DISCUSSION

The clinical and pathologic evidence that adenomatous polyps are premalignant lesions has been sufficiently convincing to most clinicians that excision of all colonic polyps has become common practice. However, that this matter was not completely settled in the minds of many physicians was emphasized in several recently published articles.

In this study 6 enzymes which are active in normal colonic mucosa were found to be less active in the polyps, and in 4 of 6 cases markedly diminished in both carcinoma in situ and in adenocarcinoma. Two of the enzymes, DPN and TPN diaphorases, were either equal to or more active in the malignant cells than in the adjacent normal epithelial cells. Our findings in normal and malignant colonic epithelium are in general agreement with those reported by Wattenberg. His descriptions of a distinctive pattern in the adenomatous polyps and the biochemical interpretations which he offers for a mechanism to control gland penetration into surrounding structures are somewhat more elaborate than is justified by both the data and the methods (9, 10). However, the more general speculations in which he indulges are indeed interesting and worthy of reiteration. The combination of high glycolytic and low cytochrome activities which have been demonstrated in cancer cells would favor the accumulation of reduced pyridine nucleotide coenzymes. Since this has not been found one might have expected increased activities of those enzyme systems resulting in the oxidation of DPNH and TPNH. The findings noted here suggest that these oxidations might be occurring through DPN and TPN diaphorases. Thus, the normal ratio of oxidized to reduced coenzymes is maintained by the transfer of electrons to other metabolites through the diaphorase systems.

The anticipation that the pattern of enzyme activities in polyps might lie somewhere between those representative of normal and carcinomatous tissues did not materialize. A somewhat similar biochemical approach has been reported by Stich and associates and Cole and McKalen by which the DNA content of polyps was compared to that of normal and malignant colonic cells. Although both groups found the DNA content of carcinoma cells to be higher than that of unchanged colonic epithelium, the DNA values for the cells in the adenomatous polyps were not strikingly different from the normal. Unfortunately, the present biochemical evidence neither supports nor refutes the view that polyps are premalignant lesions.

SUMMARY

1. Histochemical studies have been carried out on the following: 17 specimens of normal colonic mucosa, 43 adenomatous polyps, 7 carcinomas in situ, and 13 adenocarcinomas.

2. The enzymes included were representative of the hydrolytic (esterase), proteolytic (leucine aminopeptidase), and respiratory (cytochrome oxidase, succinic dehydrogenase, DPN and TPN diaphorases) activities of cells.

3. In general, the activities of these enzymes in polyps were somewhat decreased. This diminution was greater in the carcinomas with respect to esterase, leucine aminopeptidase, cytochrome oxidase, and succinic dehydrogenase. Although DPN and TPN diaphorases were reduced likewise in the polyps, their activities in the carcinomas were equal to or greater than that seen in the normal epithelial cells.

4. The findings reported herein and those contained in several recent biochemical studies neither support nor deny the concept that adenomatous polyps are precancerous lesions.

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PRODUCTION OF PORTAL HYPERTENSION IN DOGS BY A NEW METHOD

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THE PROBLEM of portal hypertension is an important one, especially in children. The initial project was to find a new operative treatment for portal hypertension by using dogs as experimental animals. Unfortunately production of a significant degree of portal hypertension in dogs was difficult, and many different methods have been attempted.

There has been interest in this subject for over a hundred years, particularly in the last quarter of a century. Rousselot in 1939 and Volwiler in 1953 injected silica repeatedly into the splenic vein of dogs attempting to produce cirrhosis and consequent portal hypertension. By this method they achieved a moderate degree of portal hypertension after about 24 months. Pearse and later Donald and Kirklin used cellophane which also produced satisfactory occlusion but only after a long interval of time. Such a long time interval limited the number of dogs that could be investigated in a reasonable length of time. It might also enable a gradual adaptation of the portal system to small rises in pressure and thus limit the final increase of portal pressure.

In 1946, Kerschner and associates produced portal hypertension by a three stage ligation of the inferior vena cava. Clatworthy and associates, in 1950, reviewed many former methods and described the extensive use of plastic bands. An ameroid was used in 1955 by Berman and associates, which produced satisfactory occlusion but the method was very slow. In 1959, Allen and Kling produced portal hypertension by reproducing the Budd-Chiari syndrome. Tamiya and Thal, in 1960, demonstrated portal hypertension after experimental splenic arteriovenous shunts and aortoportal shunts.

Only a few of the various experimental procedures used in the past were successful and most of these methods were extremely complicated technically, or involved multiple operations. In many cases only mild portal hypertension was obtained.

The normal anatomy of the portal system was studied in 10 dogs by dissection and by corrosion casts (Fig. 1). The anatomic findings from these studies were in agreement with those described by Bradley in 1927.

METHOD

Principle. In order to produce a gradual and continuous compression of the portal vein, softness of the compressing material was essential, particularly for the first few days, to allow a safety factor should a marked elevation of portal pressure occur. An irritant factor would be of value during the next few weeks to cause progressive fibrosis and render the narrowing of the vein more permanent. Such irritation might also encourage thrombosis in the narrowed lumen and organization of this thrombus would produce complete occlusion.

Material. A special, compressed sponge containing 60 per cent synthetic cellulose, with the balance of natural cellulose, including small quantities of sulfur, calcium, and magnesium was used. It was available

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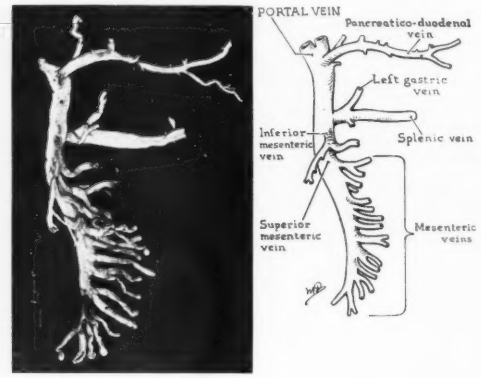


a b

FIG. 1. Normal portal system of the dog. a, Plastic cast. b, Labelled line drawing of major tributaries.

already compressed into a flat, malleable sheet which could be sterilized. An outer steel retaining ring ½ inch in diameter was lined by a thin strip of this sponge (Fig. 2a). A gap was made in the sponge ring and the metal ring. When the gaps in the sponge and metal were opposite each other, the ring could be placed so as to encircle the vein and the sponge ring could be held in position by rotating the metal ring slightly to separate the gaps. Later, the metal outer rings were replaced with nonradiopaque plastic held in place with wire loops threaded through the plastic (Fig. 2b). This enabled any narrowing of the lumen within the ring to be seen roentgenographically. Adult mongrel dogs weighing between 12 and 25 kilograms were used.

PREOPERATIVE AND POSTOPERATIVE CARE

The animals were fasted for 24 hours before operation. Atropine sulfate was injected subcutaneously, in a dose proportional to the body weight, half an hour before operation.

Anesthesia was induced in the dogs with 2½ per cent sodium thiopentone (pentothal), in a dose of 25 milligrams per kilogram of body weight. Succinyl choline chloride (anectine) was given in divided doses. After the first dose the dog was intubated and oxygen was given under controlled pressure using a T tube and, in some cases, a safety valve to prevent overinflation of the lungs. When anesthesia was complete, the operative area was shaved, washed with hexachlorophene (phisohex) followed by a double application of iodine in alcohol.

The operation was carried out with an aseptic technique. An intravenous infusion of 5 per cent glucose was maintained during the operation and anectine was administered through the tubing. Tetracycline pyrrolidinomethyl (reverin) was added to the glucose solution before the infusion was commenced, as a prophylactic antibiotic. Electrocautery was used in all operations.

DESCRIPTION OF OPERATION

The abdomen was opened through a right subcostal incision. The portal vein was exposed and freed by blunt dissection from the surrounding tissues along its length between the entry of the pancreaticoduodenal vein and the bifurcation of the portal vein as it entered the liver. The portal venous pressure was routinely measured directly in the portal vein. A venogram was made by an injection into the spleen when possible, as it was easier to control bleeding from this puncture site. The sponge and retaining ring were placed around the portal vein (Fig. 2b). A ring of the same size was used in all cases and the thickness of the sponge within the ring was constant, except in the first 2 dogs in which half the thickness of sponge was used. The operation was easy to perform and required a total time of about half an hour.

POSTOPERATIVE COURSE

The dogs recovered well postoperatively, and only 2 died of 20 subjected to the procedure. One 22 kilogram dog died 2 days after operation from acute portal hypertension due to rapid occlusion of the unusually large portal vein fitted with a standard sized ring. In the other dog the ring was placed without difficulty around the portal vein. During the operation the

spleen was attached to the abdominal wall, for later percutaneous venography, but a fatal hemorrhage occurred from the spleen.

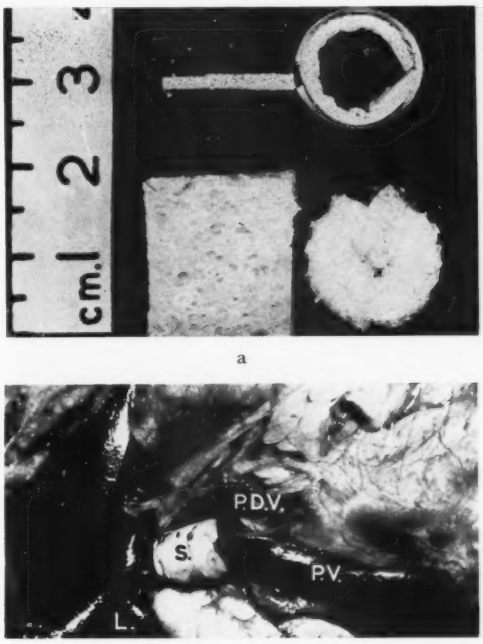
Several dogs had blood-stained vomitus for a few days after operation. During the first week the dogs were unwell, apathetic, ate poorly, and refused meat which was available. Their clinical picture resembled that reported by Riddell and associates in 1954 in an article describing hepatic coma in dogs. Serial blood ammonia determinations were made on 12 dogs. The results were inconclusive. During the succeeding weeks the appetite of the dogs improved and they began eating small amounts of meat but in spite of this fact they lost weight. In the surviving 18 dogs, investigations by laparotomy, roentgenograms, and postmortem examination were carried out.

INVESTIGATIONS

Many of the dogs had more than one laparotomy at varying intervals in order that as much information as possible could be obtained. The number and timing of laparotomies frequently depended on previous results on those dogs.

Pressure. Venous pressure readings were taken by the same operator, using the same apparatus, under uniform conditions. The pressures were taken with a spinal manometer connected to a 20 gauge needle by a polyethylene tube 30 centimeters in length. This apparatus was filled with heparinized saline. The polyethylene tubing was size 10.5 F. and measured 2.69 millimeters in internal and 3.50 millimeters in external diameter. The zero level of the spinal manometer was adjusted so that it was level with the entry of the portal vein into the liver. In each instance at least 3 readings were taken. The majority of these were made with the needle in the portal vein, although large mesenteric veins were used when the portal vein was not accessible because of adhesions.

Venograms. Hypaque 90 per cent was used as a contrast medium in all venograms. Twenty to 25 milliliters of hypaque were



a

b

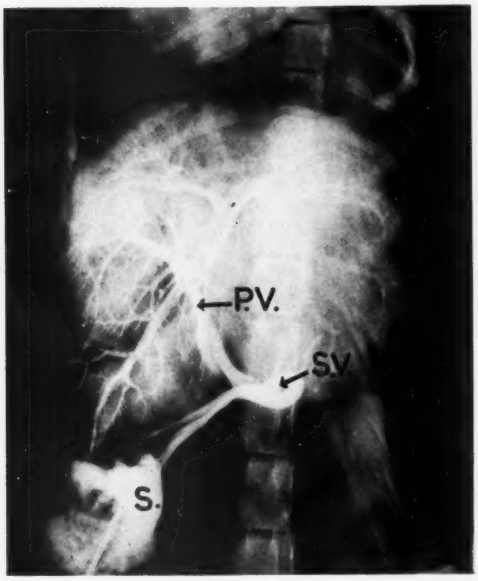
FIG. 2. Material used. a, Sponge dry and wet. The sponge expanded about 10 times when wet. The expansion was less inside the ring, pressure was greater. b, Sponge and plastic ring around the portal vein. *L.*, Liver. *P.D.V.*, Pancreaticoduodenal vein. *P.V.*, Portal vein. *S.*, Sponge.

injected gently but rapidly directly into the spleen through a 14 gauge needle using a 20 milliliter syringe. The roentgenogram was taken at the end of injection (Fig. 3).

Autopsy. A full autopsy was performed on all animals. Particular attention was paid to the development of a collateral circulation.

Corrosion casts. Corrosion casts of the collateral channels (Fig. 4) were prepared by using a colored solution of vinyl chloride plastic in acetone. This was injected into the blood vessels using red in the aorta, yellow in the portal vein, and blue in the inferior vena cava. After the plastic had set the soft parts of the specimen were digested with hydrochloric acid.

Gross examination and histology. Many of the fixed tissue slices of the portal vein



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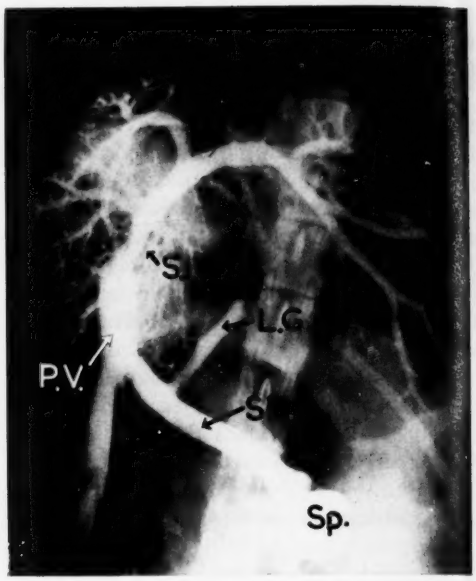

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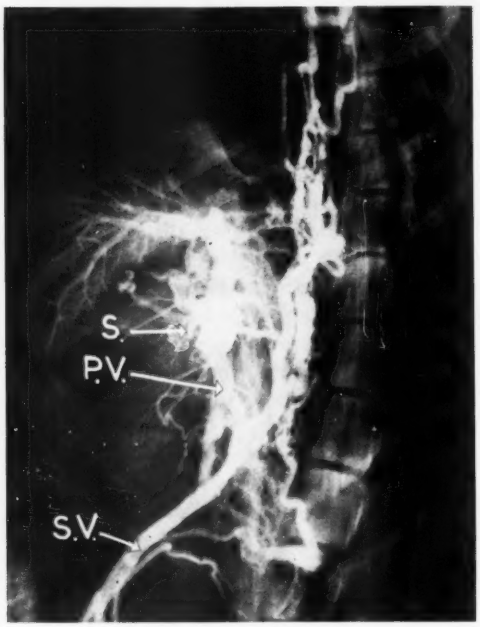

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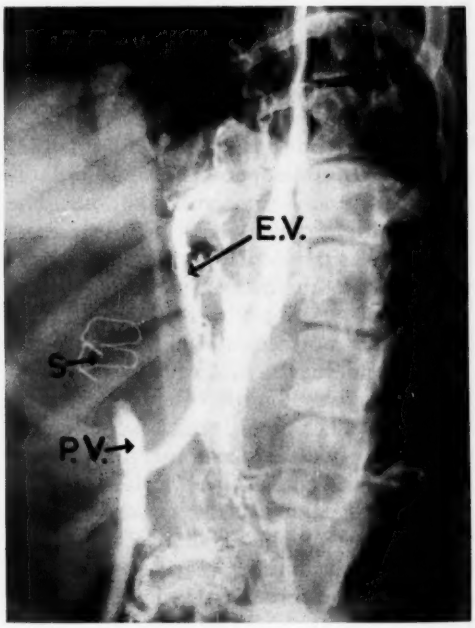
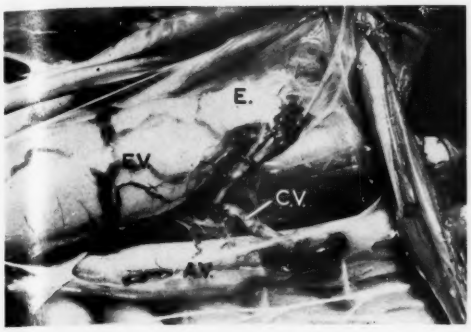


d

FIG. 3. Portograms. a, Normal venogram. b, Immediately after application of sponge. c, Development of esophageal varices. Portal vein not completely occluded at 59 days. d, Complete occlusion of portal vein at 7 days. *E.V.*, Esophageal varices. *L.G.*, Left gastric vein. *P.V.*, Portal vein. *S.*, Spleen. *S.V.*, Splenic vein, *Sp.*, Sponge.



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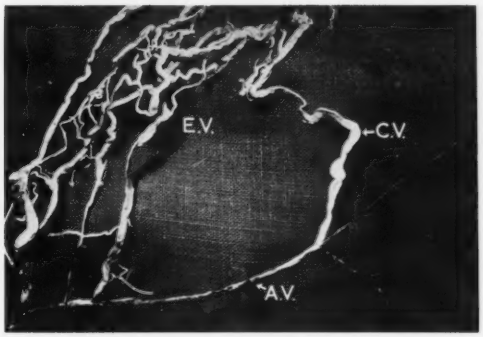

b

FIG. 4. Collateral circulation. a, Photograph of esophageal varices. b, Plastic cast of same specimen. *A.V.*, Azygos vein. *C.V.*, Collateral vessel. *D.*, Diaphragm. *E.*, Esophagus. *E.V.*, Esophageal varices.

(Fig. 5) and the details of the corrosion casts were studied with a dissecting microscope. Blocks were taken for histologic studies of normal and occluded portal veins (Figs. 5 and 6), the liver, and any tissues which appeared abnormal from the gross examination. If necessary, elastic tissue stains were added to routine stains.

RESULTS

Experimental production of portal hypertension was attempted on 20 dogs with 4 deaths, although only 1 of these deaths was due to the sponge operation. Thirteen of the remaining 16 dogs had a satisfactory range of portal hypertension, varying between 20 and 35 centimeters of water, with an average pressure of 26.5 centimeters of water. The 3 failures were due to an inadequate thickness of sponge in 2 early operations and an unusually large collateral channel in the other dog due to a previous operation.

Nine dogs had no further operations and were studied here to determine the effects of the application of the sponge to the portal vein (Table I). The other dogs will be reported elsewhere.

Portal pressure. The initial portal pressures ranged from 8.5 to 13.5 centimeters of water with an average of 9.5 centimeters of water. Pressure readings were taken postoperatively at intervals of between 1 and 20 weeks. The portal pressure remained normal in 1 dog, probably because only a half thickness sponge was used. Portal hypertension developed in the remaining 8 dogs and pressure readings ranged from 20.0 to 35.0 centimeters of water with an average pressure of 25.5 centimeters (Table I).

Portal vein. Five dogs had a complete occlusion of the portal vein. Three had an almost complete occlusion and the dog with

TABLE I.—RESULTS OF SPONGE OPERATION ON 9 DOGS

Dog No.	*Weight, kgm.*	*Reading*	*Pressure, cm. of saline*	*Days*	*Degree of occlusion*
64	15	Normal	9.5	0	−
		1st	20.0	17	+
66	12	Normal	8.5	0	−
		1st	18.0	19	+
		2nd	31.5	142	++
68	16	Normal	10.5	0	−
		1st	8.5	37	−
72	18	Normal	9.5	0	−
		1st	27.0	41	++
73	17	Normal	8.5	0	−
		1st	35.0	49	+
75	13	Normal	9.5	0	−
		1st	17.0	59	−
		2nd	20.0	90	++
76	16	Normal	9.5	0	−
		1st	22.0	12	++
81	12	Normal	13.5	0	−
		1st	21.0	7	++
		2nd	20.0	46	++
82	12	Normal	8.0	0	−
		1st	11.0	43	−
		2nd	29.0	75	+

Portal hypertension developed in 8 dogs.
++, Complete occlusion portal vein.
+, Almost complete occlusion.
−, Partial occlusion.

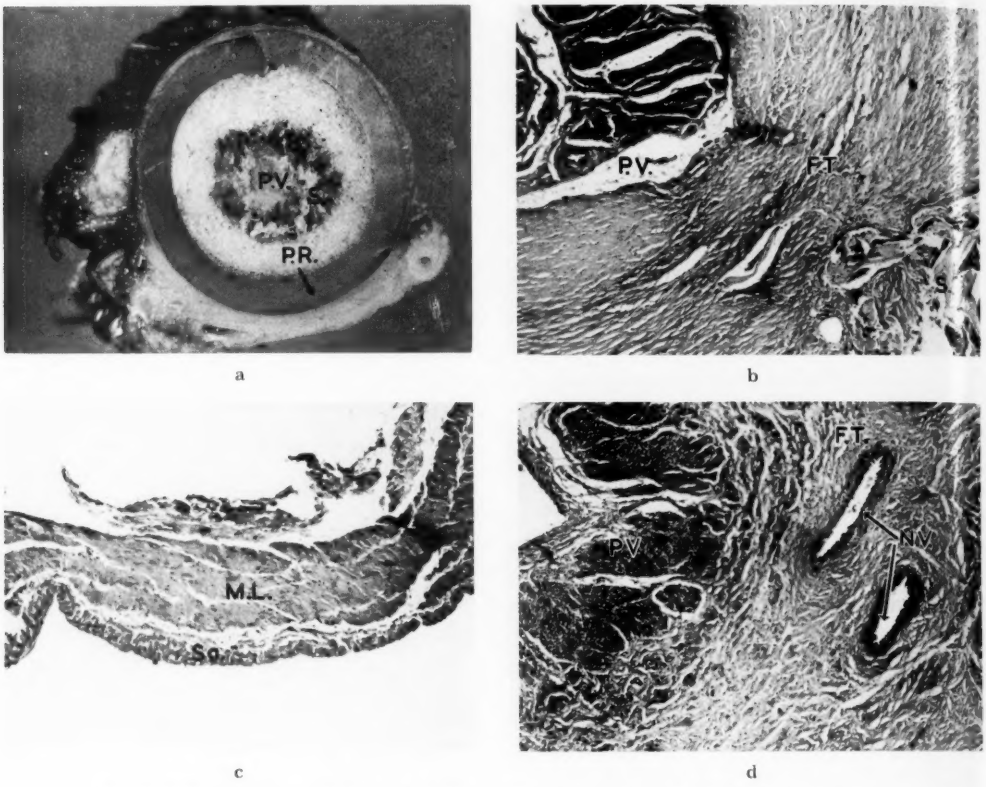

FIG. 5. Different aspects of the portal vein. a, Transverse section of occluded portal vein with ring in place (82 days) ×2. b, Dense fibrous tissue between muscle layer and sponge. ×50. c, Normal portal vein. ×20. d, Vascular fibrous tissue between muscle layer and sponge. ×50. *F.T.*, Fibrous tissue. *M.L.*, Muscle layer. *N.V.*, New vessels, *P.R.*, Plastic ring. *P.V.*, Portal vein. *S.*, Sponge. *Sa.*, Serosal layer.

a normal pressure showed marked narrowing of the vein.

Figure 6 contrasts the lumen size of a normal portal vein with the reduction and eventual obliteration produced by reaction to the sponge. A study of many specimens suggested an initial proliferation of fibrous tissue between the muscular coat and the sponge. Gradually this fibrous tissue became more dense and completely obliterated the lumen.

Collateral circulation. All the dogs showed a large collateral circulation which was best developed in those dogs with a low portal pressuré and least well developed in the dogs with the higher portal pressure. The largest collateral channel was usually the lienogastric vein. In a few instances the largest collateral vessels were those between the mesentery and the inferior vena cava.

Spleen, liver, and ascites. The spleen was normal in size in all dogs, even those with marked portal hypertension. Ascites did not develop in any of the dogs, and there were no significant changes in the liver. These findings were in agreement with Berman and Hyatt and their associates and Atkinson.

DISCUSSION

Closure of portal vein. The sponge operation occluded the portal vein in dogs in 7 to 90 days (Fig. 3). The vessels were not repeat-

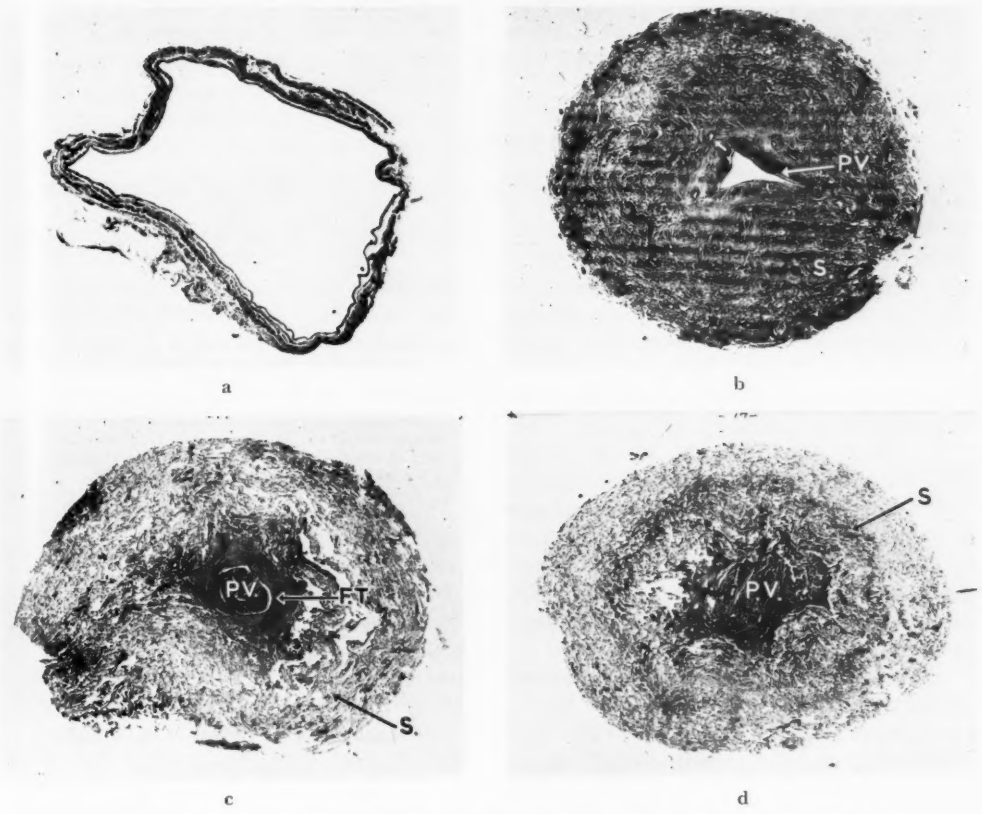

FIG. 6. Portal vein. ×4. a, Normal. b, Young fibrous tissue between sponge and narrowed vein. c, Condensation of dense fibrous tissue around muscle layer. d, Complete obliteration of lumen.

edly tested to determine the degree of closure, which partially accounted for the great range of time. The size of the metal rings and the amount of sponge—except in 2 cases—were kept constant, regardless of the size of the dogs and their portal vein. It was probably this ratio between the size of the vein and the size of the ring which determined the time required for the vein to become occluded. In dogs of approximately 20 kilograms using a ½ inch ring, the approximate time for closure of the portal vein was 3 weeks. With experience, it should be possible to vary the size of the ring and the thickness of the sponge to occlude the vein in a predicted time.

Duration of portal hypertension. The duration of portal hypertension produced by the sponge method is not known. The longest interval in this series was 142 days with a final pressure of 31.5 centimeters of water. Time limitations on the project did not permit longer observations to be made. The condition of the dogs became progressively worse after some months because of loss of weight.

Collateral circulation. From these experiments it did not seem absolutely essential to have complete occlusion of the portal vein for portal hypertension and extensive collateral circulation to develop.

A most unusual collateral channel was demonstrated in the omentum running from the spleen directly to the bladder. The ves-

sels on the abdominal wall were not unduly prominent and no caput medusae could be demonstrated.

CONCLUSION

Significant portal hypertension was produced in 8 of 9 dogs with a single easy and safe operation. The consistent degree of portal hypertension produced by this simple short operation compares extremely favorably with previous work done at this center when more classical methods of producing portal hypertension were used. Our results with Allen and Kling's method, Kershner's procedure, and the use of an ameroid were disappointing.

SUMMARY

A new easy sponge operation for the production of experimental portal hypertension has been attempted in 20 dogs with only 1 death attributable to the operation. Detailed analyses of the results in 9 of these dogs are reported here.

1. Portal hypertension was produced in 8 of the 9 dogs and ranged from 22.0 to 35.0 centimeters of water.

2. Portal hypertension frequently developed between 1 and 3 weeks after operation.

3. The duration of portal hypertension was not investigated specifically, but 146 days after operation a pressure of 31.5 centimeters of water was present.

4. No ascites was detected at any time in the dogs with portal hypertension.

5. This is a short, single operation compared with the more complicated methods described by previous workers.

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HYPOFIBRINOGENEMIA ASSOCIATED WITH PLACENTA PREVIA AND PLACENTA PREVIA ACCRETA

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AMONG the various blood coagulation abnormalities encountered in pregnancy, hypofibrinogenemia has been the subject of keenest interest. Emphasis has been placed upon the relationship between hypofibrinogenemia and abruptio placentae, prolonged intrauterine fetal death, amniotic fluid embolism, and, less commonly, infected abortions, eclampsia, and retained placenta.

This article is presented to report 6 cases of hypofibrinogenemia associated with placenta previa and placenta previa accreta. Review of the literature revealed only 3 reported cases of placenta previa complicated by hypofibrinogenemia. One case of placenta previa accreta with hypofibrinogenemia was found. Placenta previa accreta itself is an uncommon complication of pregnancy and according to Foster only about 50 cases have been reported in the literature.

MATERIALS AND METHODS

The 6 cases reported here have been collected from approximately 20,000 deliveries attended from 1956 to 1960 at the Sloane Hospital for Women. The diagnosis of placenta previa was established at the time of cesarean section. The criteria for the diagnosis of placenta previa accreta have been the presence of villi within the myometrium and the absence of a decidua basalis.

The following methods for studying the blood plasma factors have been used: fibrinogen by the method of Ratnoff and Menzie; clot lysis, the observation of serially diluted plasma clots according to a modified Coon's method; free profibrinolysin by hydrolysis of casein by plasma activated with streptokinase, after Phillips and Skrodelis (12); total profibrinolysin by hydrolysis of casein by an isoelectric precipitate from plasma activated with streptokinase (12); inhibitors, by the difference between the total and free profibrinolysin (12); and prothrombin, after Quick; proaccelerin; prothrombin consumption time, by the test of Sussman and associates; and thromboplastin generation time, after Biggs and Duckert and their associates.

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CASE REPORTS

CASE 1. A 35 year old Negro female, gravida 6, para 5, was admitted on 14 March 1960 for an elective quaternary cesarean section because of a vaginal plastic operation. The previous antepartum course had been uneventful.

Pelvic examination was performed at 2 p.m. on the day of admission to ascertain fetal presentation. This examination resulted in a sudden profuse hemorrhage of approximately 1,500 milliliters. An emergency classical cesarean section was performed within 5 minutes, delivering a 3,100 gram living female infant from the vertex presentation. A central placenta previa was encountered which was difficult to separate because of a poor cleavage plane, especially in the central area over the cervix. The placenta was removed in fragments. Profuse hemorrhage continued. From the beginning of the operation the patient was in profound shock. Systolic blood pressure of 60 millimeters of mercury was obtainable only by palpation. Dextran and plasma were rapidly infused, followed by blood when available.

After closure of the abdomen, vaginal bleeding continued. Pelvic examination revealed placental tissue adherent to the endocervix and lower uterine segment. A curettage was performed and the uterus was packed. It was noted that the patient was bleeding from vari-

TABLE I.—COAGULATION STUDIES IN CASE 1

	14 March 8:00 p.m.	*15 March 8:00 a.m.*
Fibrinogen	107 mgm. per cent	161 mgm. per cent
Prothrombin time, control 13	26 secs.	16 secs.
Factor V	10 to 20 per cent normal	100 per cent normal
Factor VII	Decreased	Normal
Prothrombin consumption time	13 secs.	20 secs.
Thromboplastin generation	CLOTTING TIME	
Patient's plasma and serum		
2 mins.	24 secs.	12 secs.
4 mins.	30 secs.	10 secs.
6 mins.	30 secs.	11 secs.
Patient's plasma and normal serum		
2 mins.	16 secs.	
4 mins.	16 secs.	
6 mins.	19 secs.	
Normal plasma and patient's serum		
2 mins.	13 secs.	
4 mins.	14 secs.	
6 mins.	15 secs.	

ous vein puncture sites and the abdominal incision. Fibrinogen at 4:30 p.m. after 2½ hours of shock was 65 milligrams per cent. There was 6 plus clot lysis and profibrinolysin and inhibitors were depressed. Fibrinogen was administered intravenously in large amounts. In addition to blood, toluidine blue, mephyton, and calcium gluconate were given. The uterus was repacked because of continued bleeding. Six hours after the initial episode, vital signs began to stabilize with blood pressure of 90/60 millimeters of mercury; clot formation appeared; fibrinogen was 107 milligrams per cent; and hematocrit was 35 per cent. Profibrinolysin and inhibitors were virtually absent. By this time, the patient had received a total of 1,700 milliliters of dextran, 500 milliliters of plasma and 5,500 milliliters of blood, of which 1,500 milliliters was fresh blood, and 16 grams of fibrinogen. By midnight the patient had received an additional 1,500 milliliters of fresh blood and 4 grams of fibrinogen.

On the first postoperative day fibrinogen was 161 milligrams per cent; profibrinolysin and inhibitors were still markedly below normal. Urine output was 720 milliliters and the blood urea nitrogen was 25 milligrams per cent. Hematocrit was 28 per cent.

On the second postoperative day, upon removal of uterine packing, profuse vaginal bleeding ensued. The patient, again in a state of borderline shock, was taken to the operating room where an emergency hysterectomy was performed. The preoperative fibrinogen level of 340 milligrams per cent fell to 213 milligrams per cent postoperatively, in spite of 1,000 milliliters of plasma, 4,500 milliliters of blood and 6.0 grams of fibrinogen. Hematocrit was 40 per cent. On the following day the patient was alert with stable vital signs; urine output was adequate; blood urea nitrogen reached a peak level of 54 milligrams per cent on the second postoperative day and slowly returned to normal.

Follow-up studies showed an inability to concentrate urine in response to fluid deprivation and antidiuretic hormone. No evidence of anterior pituitary dysfunction was obtained. Pathologic examination disclosed placenta previa, placenta accreta, and placenta increta.

This patient manifested severe hypofibrinogenemia with fibrinolytic activity and decrease in profibrinolysin and inhibitors after hemorrhagic shock. Despite the administration of exceedingly large amounts of fibrinogen during the state of shock, coagulation was not established. As shock was corrected by transfusion of fresh and stored blood, fibrinogen level began to rise and blood clotting commenced. Table I shows depletion of other coagulation factors. Most of these had returned to normal levels within 12 hours. The fall of fibrinogen, profibrinolysin, and inhibitors during the second operation in spite of 6 grams of fibrinogen and complete blood replacement indicates that active fibrinolysis had again occurred.

CASE 2. A 36 year old white female, gravida 6, para 2, whose expected date of confinement was 10 July 1956, was admitted on 11 June with painless vaginal bleeding. The previous antepartum course had been uneventful. The past history revealed 3 spontaneous abortions, a primary cesarean section for placenta previa at 6 months gestation, and a secondary cesarean section for placenta previa at 8 months gestation.

On 16 June the patient had onset of increased vaginal bleeding and mild lower abdominal pain. A classical cesarean section was performed at 2:40 p.m. delivering a 2,980 gram living female infant from the vertex presentation. A central placenta previa adherent to the lower uterine segment was encountered and had to be removed in fragments. Massive bleeding which immediately ensued from the implantation site failed to respond to oxytocics and uterine massage. Accordingly, a subtotal hysterectomy was performed. During the procedure, the patient went into profound shock. No peripheral pulse or blood pressure was obtainable for approximately 45 minutes in spite of rapid administration of dextran and blood. After shock had been present for 1 hour and 45 minutes a blood sample for fibrinogen determination was drawn.

The level was later found to be 84 milligrams per cent. After the administration of 1,500 milliliters of dextran and 4,500 milliliters of blood, of which 2,500 milliliters were freshly drawn, the blood pressure finally returned to normotensive values and bleeding subsided. No fibrinogen was administered. At 10 p.m. the fibrinogen was 135 milligrams per cent. The postoperative course was benign. Pathologic examination revealed placenta previa.

This patient represents an example of moderate hypofibrinogenemia. After the correction of hemorrhagic shock by administration of fresh and stored blood the fibrinogen level rose without administration of fibrinogen. Profibrinolysin and inhibitors, which were depleted during the hemorrhagic episode, also returned to normal.

CASE 3. A 35 year old white female, gravida 3, para 2, with 3 August 1958 as the expected date of confinement, was admitted at 3 a.m. on 25 July with painless vaginal bleeding. The antepartum course had been benign except for two episodes of vaginal spotting in the third trimester. There was a past history of a normal full term spontaneous delivery and a classical cesarean section for fetal distress and placenta previa. At 7 a.m. a classical cesarean section was performed, delivering a 2,610 gram living female infant from the vertex presentation. A placenta previa was encountered as well as an occult rupture of the previous cesarean section scar. The placenta was removed with difficulty as it was firmly attached to the lower uterine segment and cervix. Brisk bleeding ensued from the uterine incision and implantation site; the patient went into shock with a blood pressure of 50/20 millimeters of mercury. Supracervical hysterectomy was performed. The patient received 1,000 milliliters of dextran and 2,000 milliliters of blood during the operation, which was completed at 9:30 a.m. The fibrinogen was 138 milligrams per cent. The patient continued to bleed profusely from the vagina and the blood pressure remained at shock levels. Two grams of fibrinogen were given at 11 a.m. At 11:30, the fibrinogen was 156 milligrams per cent. Vaginal and cervical stump packing failed to control bleeding adequately. By 1 p.m. the patient had received a total of 5,500 milliliters of blood. At 3 p.m. blood pressure finally returned to normotensive levels and vaginal bleeding slowly subsided; the fibrinogen was 194 milligrams per cent. The postoperative course was benign. The pathologic study showed placenta previa accreta and placenta increta.

This case is an example of mild hypofibrinogenemia associated with depression of total profibrinolysin and inhibitors. The poor response to fibrinogen and the additional decrease in profibrinolysin and inhibitors suggest that activation of the fibrinolytic system was continuing during the hemorrhagic phase. After correction of shock all values returned toward normal.

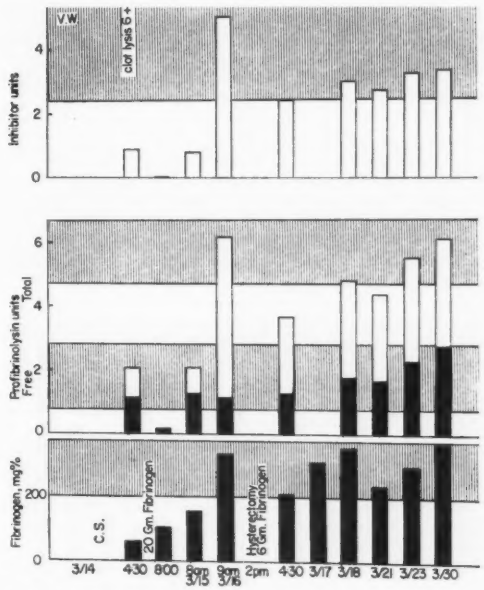

FIG. 1. Laboratory studies of the fibrinolytic enzyme system for the patient in Case 1.

CASE 4. A 35 year old Negro female, gravida 3, para 1, was admitted on 15 December 1958 for elective secondary cesarean section. There was a past history of a cesarean section for absolute cephalopelvic disproportion and a spontaneous abortion. The antepartum course was benign. On 24 December at 8 a.m. a section was performed, delivering a 3,710 gram living male infant from breech presentation. A marginal placenta previa adherent to the lower uterine segment was encountered. Manual separation was incomplete and massive bleeding from the implantation site ensued, which was only partially controlled by deep sutures. At 10 a.m. the blood pressure fell to 80/50 millimeters of mercury and the patient remained in shock for 1½ hours. Fibrinogen at 11 a.m. was 189 milligrams per cent. Bleeding was noted from all cut surfaces. During the operation 2 grams of fibrinogen were administered, raising the level to only 206 milligrams per cent. The patient received 1,000 milliliters of dextran and a total of 2,500 milliliters of blood. Postoperatively, vaginal bleeding continued, necessitating additional blood transfusions and 1 gram of fibrinogen. Hematocrit on the first postoperative day was 25.6 per cent. The remaining

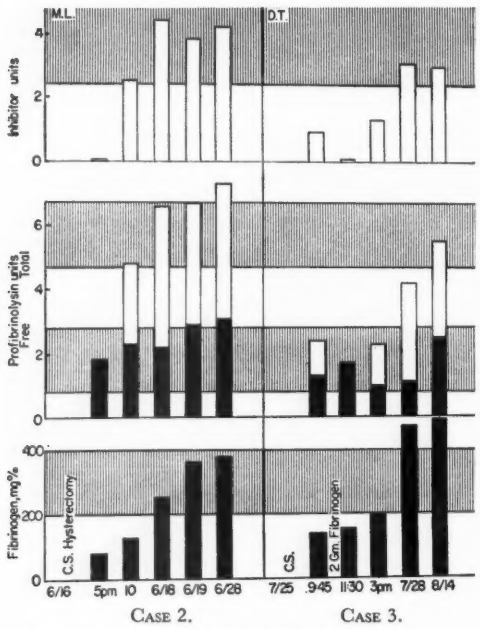

FIG. 2. Laboratory studies of the fibrinolytic enzyme system for the patients in Cases 2 and 3.

postoperative course was benign. Pathologic examination revealed placenta circummarginata and placentitis.

This case is of interest because, after the episode of hemorrhagic shock, the original fibrinogen level was not markedly depressed. Despite the administration of 2 grams of fibrinogen, falling levels of fibrinogen, profibrinolysin, and inhibitors suggest that a fibrinolytic process was taking place which gradually reversed itself after cessation of bleeding.

CASE 5. A 30 year old white female, gravida 2, para 0, whose expected date of confinement was 5 July 1956, was admitted on 31 May with painless vaginal bleeding. There was a past history of compensated inactive rheumatic heart disease with mitral insufficiency, a right oophorectomy, and a spontaneous abortion.

The fibrinogen level on 4 June was 325 milligrams per cent. On 25 June after a pelvic examination, profuse vaginal bleeding ensued and an emergency classical cesarean section was performed at 8:50 a.m., delivering a 3,600 gram living male infant. A central placenta previa was removed intact. There was extreme blood loss from large venous sinuses at the implantation site. During the operation the blood pressure was at shock levels for approximately 45 minutes. The patient received 500 milliliters of dextran and 1,000 milliliters of blood.

Postoperatively, vaginal bleeding continued and blood pressure remained at hypotensive level for approximately 6 hours. Fibrinogen at 11 a.m. was 161 milligrams per cent. By 3 p.m. the patient had received 2,500 milliliters of whole blood and fibrinogen was 182 milligrams per cent. The postoperative course was benign.

This patient had a normal fibrinogen level preoperatively and mild hypofibrinogenemia developed, presumably within a period of 2½ hours. Six plus clot lysis was demonstrated. Shock was treated with transfusions. No fibrinogen was administered.

CASE 6. A 30 year old white female, gravida 3, para 1, with the expected date of confinement in mid-September 1956, was admitted on 27 June for painless vaginal bleeding and premature rupture of the membranes. There was a previous history of a cesarean section for absolute cephalopelvic disproportion and a spontaneous abortion.

Fibrinogen level 20 July was 330 milligrams per cent. On 24 July at 11 a.m. profuse vaginal bleeding occurred with the loss of approximately 1,000 milliliters of blood. The patient went into shock with a blood pressure of 80/0 millimeters of mercury. An emergency classical cesarean section was performed, delivering a 1,608 gram living female infant. A central placenta previa was encountered which was easily removed intact. The patient received 500 milliliters of dextran and 1,500 milliliters of whole blood during the operation. A fibrinogen level at 4:30 p.m. was 187 milligrams per cent. Only slight vaginal bleeding was observed postoperatively and recovery was uneventful.

This patient exhibited only a mild degree of hypofibrinogenemia associated with transient shock due to moderate blood loss. Postoperatively there was some decrease in profibrinolysin and inhibitor levels.

DISCUSSION

Incidence. It is surprising that the association of hypofibrinogenemia with placenta previa and placenta previa accreta has been reported so rarely. The occurrence of hypofibrinogenemia at the Sloane Hospital for Women is 50 cases per 20,000 deliveries in a 4½ year period. The cases of hypofibrinogenemia reported represent 12 per cent of

all cases of hypofibrinogenemia seen in this institution. In contrast to this incidence, a group of 48 cases of hypofibrinogenemia reported from the Los Angeles County Hospital by Longo and associates within a 6 year period contained no cases associated with placenta previa.

An explanation as to why this condition has been previously so infrequently observed is purely speculative. One reason may be that in this institution clotting studies are performed on all obstetric patients in whom significant bleeding of any kind is encountered. If the custom were to obtain these studies only of patients with conditions known to have associated clotting deficiency, such as abruptio placentae, amniotic fluid embolism, or dead fetus syndrome, the more unusual conditions might very well be missed. It would seem that if routine studies were performed on all patients with hemorrhage occurring in pregnancy, this association would be more commonly observed. The depression of fibrinogen in many of the cases of placenta previa, although moderate, is not associated with general hemorrhagic manifestations, seems to be transient, and is often corrected by the administration of blood given in response to the shock and to acute blood loss.

Etiology. Hypofibrinogenemia is the term commonly applied to a group of conditions associated with the depression of blood fibrinogen levels and other defects such as thrombocytopenia, hypoprothrombinemia, proaccelerin deficiency, and increased plasma fibrinolytic and antithrombic activity. There are two principal mechanisms that have been suggested as the cause of hypofibrinogenemia. One theory, suggested by Schneider, is that the decrease in fibrinogen level is caused by intravascular clotting resulting from the introduction of thromboplastin-like substances from the uterus into the maternal circulation. The other theory, of Phillips and associates (11), suggests that the mechanism for depletion of fibrinogen is its removal by hydrolysis by a fibrinogenolytic enzyme. We suggest that the latter

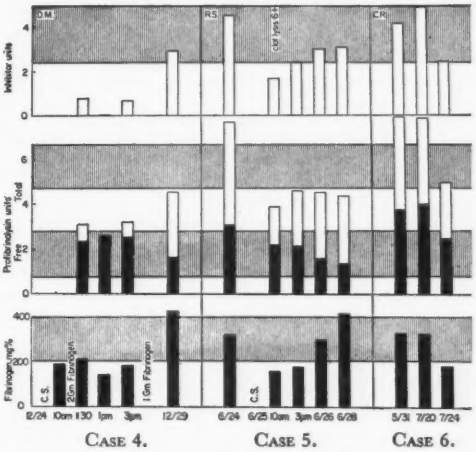

FIG. 3. Laboratory studies of the fibrinolytic enzyme system for the patients in Cases 4, 5, and 6.

mechanism is the most important factor in the cases reported herein.

As early as 1893, the French biochemist Dastre postulated that fibrinogen was decreased after phlebectomies in dogs as a result of actual destruction or lysis of fibrin and coined the term fibrinolysis. Subsequently, many investigators have partially clarified the process of fibrinolysis as described in excellent reviews by MacFarlane and Biggs and more recently by both Astrup and Sherry and associates. The current concept of fibrinolysis as outlined in Figure 4 envisages an enzyme system which consists of an active enzyme, fibrinolysin or plasmin, its precursor, profibrinolysin or plasminogen, and its inhibitors, antifibrinolysin or antiplasmin. Proactivator is also present, as either a separate molecule or an additional activity of the profibrinolysin molecule.

Fibrinolysin and profibrinolysin are found in the euglobulin fraction of plasma, whereas the antifibrinolysin is associated with the albumin and alpha globulins. Fibrinolysin is not specific in its proteolytic activity but is capable of digesting fibrin, fibrinogen, prothrombin, proaccelerin, casein, gelatin, and other proteins.

Previous studies have indicated that shock may precipitate the activation of the

TABLE II.—SUMMARY OF CASES OF HYPOFIBRINOGENEMIA ASSOCIATED WITH PLACENTA PREVIA OR PLACENTA PREVIA ACCRETA

Case No.	*Duration of shock, minutes*	*Lowest fibrinogen, mgm. per cent*	*Fibrinogen given, gm.*	*Blood, ml.*	*Dextran, ml.*	*Accreta*	*Additional operation*	*Other bleeding manifestations*
1	1) 330	65	20	7000	1700	Yes	None	Yes
	2) 45	213	6	4500	—	—	Hysterectomy	No
2	105	84	None	2500	1500	No	Hysterectomy	Yes
3	150	138	2	5500	1000	Yes	Supracervical hysterectomy	No
4	90	138	3	4000	1000	No	None	Yes
5	45	161	None	4000	1000	No	None	No
6	30	187	None	1500	500	No	None	No

fibrinolytic system with the resultant conversion of profibrinolysin to fibrinolysin. Studies by Tagnon and coworkers in 1946 described excessive fibrinolytic activity resulting from both clinical and experimentally induced shock. In the experimental hemorrhagic shock produced in dogs, they demonstrated a marked and progressive fall in the levels of fibrinogen and prothrombin. They speculated that the fibrinolytic enzymes might arise from plasma or could arise from the cellular elements of damaged tissue as suggested by higher levels of fibrinolytic activity in venous rather than arterial blood. Stefanini and Turpini showed in hemorrhagic shock studies in rabbits an early fall in fibrinogen levels with a rise in platelets and fibrinolysin followed by a later fall in platelets and factor V.

Astrup outlines two mechanisms in the human for the initiation of fibrinolytic activity. The first consists of an interaction between profibrinolysin and an activator released from injured tissue. This process is a local one and is probably responsible for the resolution of local fibrin deposits and for tissue repair. The second activation mechanism changes a proactivator in blood to an activator. This activator is formed very rapidly, probably by means of a soluble lysokinase existing in certain tissues, and is then carried to all organs. This process, therefore, is of a general character. The lysokinase probably originates in tissue cells, and shock may, in an as yet unknown fashion, liberate this enzyme, thereby activating the fibrinolytic system. Astrup was able to find a component with the properties described in certain samples of human kidney tissue. Kwaan and MacFadzaen have suggested that activator is released from vessel walls secondary to ischemia. This is consistent with the view expressed by Tagnon that shock stimulates fibrinolytic activity.

It is apparent then, that such a kinase circulating in the blood stream is capable of producing serious alterations in the coagulation mechanism and causing potentially fatal hemorrhages. A vicious cycle can be established in which shock may alter the plasma factors of hemostasis. This in turn may result in further loss of blood, thereby augmenting shock. (Fig. 5).

Another mechanism for the initiation of fibrinolysis may be the general stress reaction resulting from the hemorrhagic shock with the subsequent release of adrenal hormones. MacFarlane and Biggs demonstrated that such diverse stimuli as fear, exercise, trauma, and surgery, as well as the administration of adrenalin may produce excessive fibrinolytic activity. Margulis and associates have demonstrated an increased plasma fibrinolytic activity associated with normal parturition.

The studies of the fibrinolytic system of the 6 patients presented here have shown that not only does the fibrinogen level fall but the total profibrinolysin and inhibitor levels also decrease. This is interpreted as evidence that the precursor was activated during this period and that the active enzyme hydrolyzed the fibrinogen in the

blood stream. Although plasma clot lysis was demonstrated in only 2 patients, those in Cases 1 and 5, it must be remembered that the enzymes involved in this system are exceedingly labile and are easily and rapidly inactivated both in vitro and in vivo.

Therefore, it is suggested that the common factor in hypofibrinogenemia associated with placenta previa is the shock resulting from the massive hemorrhage from the abnormal implantation site. Placenta previa and placenta previa accreta can result in sudden and profuse hemorrhage as is well demonstrated in the cases presented. The sudden fall in blood pressure, and the subsequent general tissue anoxia might well cause an activation of the fibrinolytic system as outlined herein.

Blood loss alone does not seem to be the cause of the acquired hypofibrinogenemia as suggested by Rocker. Although the subsequent hemodilution and the administration of stored blood tend to lower fibrinogen levels somewhat, these factors cannot explain the strikingly low fibrinogen values observed in some of these patients. Analysis of these cases suggests that the fibrinogen depletion as well as the other demonstrated deficiencies in coagulation mechanism parallels the degree of shock and possibly its duration (Table II). Case I is particularly interesting in view of the large amounts of fibrinogen given. Despite the administration of 20 grams of fibrinogen, only a slight rise in the fibrinogen level was seen, indicating a continuous lysis. After correction of blood loss by administration of fresh and stored blood, and after the patient had become consistently normotensive, some clot formation was seen, the fibrinogen level rose, bleeding subsided, and enzymatic activity returned toward normal. On the basis of the view that hypofibrinogenemia is due to excessive intravascular clotting it would be expected that widespread fibrin deposition with vessel occlusion should have occurred after the administration of such amounts. There was no clinical evidence of such complications. Also, with placenta

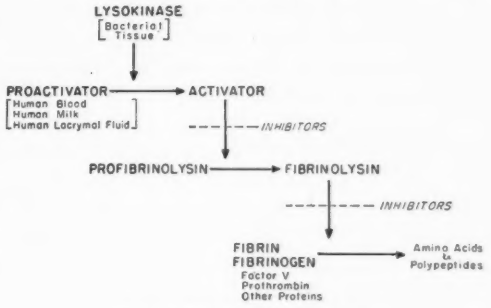

FIG. 4. The fibrinolytic system.

previa, unlike abruptio placentae, the conditions are inappropriate for a mechanism of thromboplastin infusion into the maternal circulation, because there is no concealed hemorrhage. Therefore, it is unlikely that the hypofibrinogenemia in patients with hemorrhagic shock associated with placenta previa is due to thromboplastin release and fibrin deposition.

Management. Of the 6 cases presented here, fibrinogen replacement therapy was instituted in only 3. Treatment of shock by blood replacement and other supportive measures often sufficed to reverse the fibrinolytic phenomenon. This management is consistent with the previously advanced hypothesis that the hypofibrinogenemia is brought about by activation of the fibrinolytic system by tissue anoxia that follows hemorrhagic shock. In our experience, fresh blood in addition to stored blood may be of critical importance. In patients with markedly decreased fibrinogen levels and prolonged hemorrhagic shock, large amounts of fibrinogen may be required.

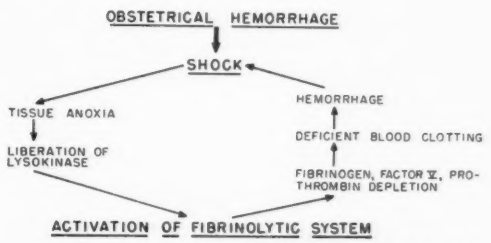

FIG. 5. Proposed scheme for activation of fibrinolytic system by hemorrhage.

The value of administration of inhibitors such as epsilon-amino caproic acid, toluidine blue, and soybean trypsin inhibitors remains to be established.

The use of large amounts of dextran is frequently inevitable, but it should be noted that dextran, according to Scott, may exert an unfavorable effect on the coagulation mechanism. Plasma or albumin should therefore be given preference in treatment of shock until blood is available.

In cases of placenta previa accreta it has been consistently demonstrated that hysterectomy is the treatment of choice to control uterine bleeding.

SUMMARY

Six cases of placenta previa, 2 complicated by placenta accreta, are presented with the clinical picture of hemorrhagic shock and demonstration of hypofibrinogenemia.

It is suggested that the hypofibrinogenemia and other coagulation defects are brought about by activation of the fibrinolytic system by tissue anoxia that follows hemorrhagic shock. Laboratory studies supporting such a conclusion are presented.

The importance of the correction of shock in addition to the administration of fresh blood and fibrinogen is emphasized.

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THE EFFECT OF KIDNEY HYPERTHERMIA ON RENAL TOLERANCE TO TOTAL ISCHEMIA

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THE PROTECTIVE EFFECT of local cooling of the kidney has been substantiated by Bogardus, Moyer, and Stueber and their associates and in this laboratory (7). The decrease in tissue metabolism and oxygen requirement at lower than body temperature prolongs the permissible period of ischemia. In extension of our previous studies, the present investigation was undertaken to evaluate the possible limiting effect of local warming of the kidney and systemic hyperthermia on the permissible period of renal ischemia.

MATERIALS AND METHODS

In situ kidney warming after contralateral nephrectomy in dogs. Twenty-one male and female mongrel dogs weighing between 9 and 16 kilograms were employed. After anesthesia with intravenous sodium pentobarbital, 30 milligrams per kilogram, a right nephrectomy was performed through a midline abdominal incision. The left kidney was freed from its capsule, and the artery, vein, and ureter were isolated and occluded with atraumatic bulldog clamps. Just before clamping of the artery, 1,000 units of heparin sodium were injected into the artery to prevent thrombosis. The kidney was inverted into the bottom of a sterile watertight polyethylene bag previously described (7), so that it could be maintained at either 37.5 or 41 degrees C. but would not be in direct contact with the warming solution, 0.85 per cent saline. Occlusion times varied from ½ hour to 2 hours. After the clamps were removed the abdomen was closed and the animal was allowed to recover. Ten per cent dextrose in water was administered intravenously as needed for 2 to 3 days after the surgical procedure. Serum creatinine concentrations, urine volumes, and urine specific gravities were determined serially for 2 weeks. Autopsy and histologic studies of the kidney were made on each animal.

The time required for kidney temperature to reach equilibrium with the warming solution was determined by using a thermistor in the renal parenchyma.

In situ kidney warming and delayed contralateral nephrectomy in dogs. Seven dogs, weighing between 10 and 14 kilograms, were employed. The procedure was the same as previously described, except that the contralateral (right) nephrectomy was delayed 3 weeks to allow recovery of the animals. The kidney temperature in each animal was maintained at 37.5 degrees C., occlusion times varying between 1 and 2½ hours. The contralateral nephrectomy was performed through a flank muscle-splitting incision under sodium pentobarbital anesthesia. Serum creatinine concentrations, urine volumes, and urine specific gravities were determined serially for 2 weeks.

Systemic hyperthermia in rabbits. Seventeen New Zealand white rabbits, weighing between 1.0 and 1.8 kilograms, were employed. Sodium pentobarbital, 25 milligrams per kilogram, was administered in a peripheral ear vein. The febrile response to intravenous Shigella flexneri endotoxin, 0.005 milligram per kilogram, was deter-

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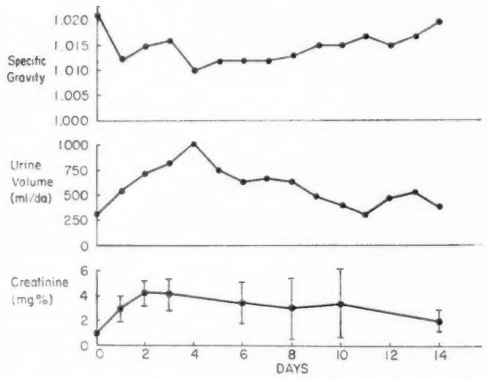

FIG. 1. Recovery from renal pedicle occlusion was characterized by an early decrease in the average urine specific gravity and increase in the average volume output. Serum creatinine was highest between the second and third days. Mean values are graphed with 1 standard deviation of the creatinine levels indicated.

mined in normal rabbits by serial measurements of rectal temperature. In all animals the renal capsule was stripped, and the artery, vein, and ureter were isolated bilaterally.

In group 1, 4 rabbits were used. The renal artery and ureter were clamped atraumatically for 2 hours and the incision was closed. The animals were returned to their cages and allowed to recover.

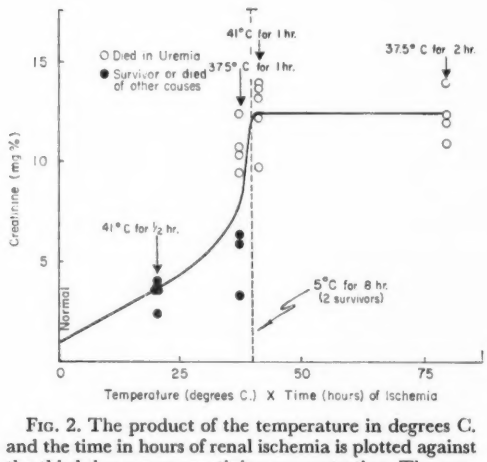

FIG. 2. The product of the temperature in degrees C. and the time in hours of renal ischemia is plotted against the third day serum creatinine concentration. The contralateral nephrectomy in this group of dogs was performed before the period of ischemia.

Group 2 consisted of 3 rabbits. Shigella flexneri endotoxin, 0.005 milligram per kilogram, was given intravenously 1 hour before the operative procedure. The renal artery and ureter were not clamped. The incision was closed and the animals were returned to their cages and allowed to recover.

Group 3 consisted of 7 rabbits. Shigella flexneri endotoxin, 0.005 milligram per kilogram, was given intravenously 1 hour before renal artery and ureter occlusion. The clamps were removed after 2 hours, the incision was closed, and the animals were returned to their cages to recover.

RESULTS

Direct measurement of the kidney temperature in dogs indicated equilibrium with the bath temperature at 41 degrees C. in approximately 10 minutes. After contralateral nephrectomy, with total ischemia for ½ hour and the kidney at 41 degrees C., none of the animals died in uremia, but, with ischemia for 1 hour at this elevated temperature, all the animals died in uremia. After 1 hour of renal ischemia at 37.5 degrees C., 4 of 7 animals died in uremia, whereas after 2 hours of ischemia at this normal body temperature, all the animals became anuric and died.

Recovery from renal pedicle occlusion was characterized by an early decrease in specific gravity of the urine and an increase in urine volume. Serum creatinine concentration was highest between the second and third days (Fig. 1).

Values for the product of the temperature and occlusion time correlated well with the survival rate and the third day serum creatinine concentration, as shown graphically in Figure 2. The third day creatinine values were utilized because they represented the highest levels in most of the surviving animals. The average serum creatinine value increased sharply at 40 degree hours. The surviving animals are grouped below this level. The difference between the averages of the third day serum

creatinine concentrations of the dogs with ischemia for 1 hour at 37.5 and at 41 degrees C. is statistically significant (P = 0.025).

After delayed contralateral nephrectomy, with total renal ischemia for 1½ hours or less and the kidney at 37.5 degrees C., none of the animals died in uremia. With renal ischemia for 2 hours or more, all of the animals became anuric and died. Values for the product of the temperature and occlusion time are related to the third day serum creatinine concentrations as shown in Figure 3. The curve from Figure 2 has been superimposed to show its relationship.

Histologic examination of the kidneys of the surviving animals which had had the contralateral nephrectomy before the ischemic period revealed no significant lesion in the glomerular tufts and little change in the proximal tubular cells. In the medulla, however, there was marked cloudy swelling and areas of cellular death, hyaline casts in the tubules, and slight leukocytic infiltration which have been described by Karsner in acute nephrosis. In the animals which died in uremia, both the cortex and the medulla showed marked cloudy swelling of the tubular cells and in most areas there was disintegration of the nuclei, indicating cell death. Hemorrhage into the interstitial tissue was observed in the latter group.

The kidneys of the surviving dogs which had had a delayed contralateral nephrectomy revealed a histologic picture similar to the first group. However, in the animals which died there were only a few remaining tubules containing hyaline casts, areas of chronic inflammatory cells, and marked fibrous tissue replacement.

In the rabbit studies, the febrile response after intravenous injection of Shigella flexneri endotoxin was characterized by a peak, between 3 and 4 hours, followed by a gradual decline to normal in about 12 hours (Fig. 4). Nearly all of the animals tolerated either the endotoxin infusion or the 2 hour period of bilateral renal ischemia but all of the animals died in uremia after being subjected to both procedures.

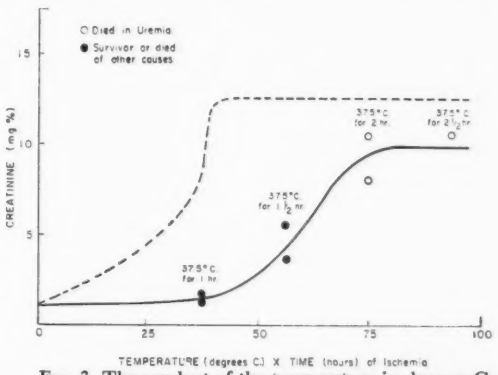

FIG. 3. The product of the temperature in degrees C. and the time in hours of renal ischemia is plotted against the third day serum creatinine concentration. The contralateral nephrectomy in this group of dogs was delayed 3 weeks. The dotted line represents the curve from Figure 2.

DISCUSSION

Du Bois in 1921 documented the increase in basal metabolism with increase in body temperature. A rise of 1 degree F. increases metabolism about 7 per cent. Increased oxygen consumption of the dog and canine cardiac muscle during fever has been verified. During fever the elevation of body temperature is the cause of increased metabolism, since an increased metabolic rate preceding the fever does not occur. The

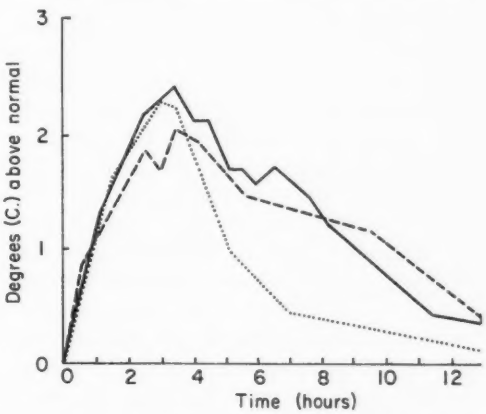

FIG. 4. The febrile response in rabbits after intravenous injection of Shigella flexneri endotoxin, 0.005 milligrams per kilogram, reaches a peak at between 3 and 4 hours.

increase in metabolism with rise in temperature exemplifies van't Hoff's law that the velocity of a chemical reaction increases approximately two times for a temperature rise of 10 degrees C. This would imply that the tissue metabolic rate would be increased by 40 to 50 per cent with a temperature elevation from 37.5 to 41 degrees C.

This study verifies the hypothesis that local and systemic hyperthermia, in the range of the physiologic febrile response, causes a reduction of the permissible period of renal ischemia. With the kidney at 41 degrees C. and previous contralateral nephrectomy, all of the dogs died of uremia after 1 hour of renal ischemia, whereas at 37.5 degrees C. and the same ischemic period, only half of the animals died of uremia.

Under these conditions, a critical limiting temperature time range, 35 to 40 degree hours, was determined for survival of the ischemic dog kidney. The validity of this concept was substantiated in the previous studies (7) to determine the protective effect of local cooling of the kidney to 5 degrees C. It was found that survival was possible with up to 8 hours of ischemia. This end-point is represented in Figure 2 by the vertical dotted line placed at 40 degree hours.

With the method utilized in this experiment, including division of the capsular vessels and occlusion of the ureteral artery, renal artery, and renal vein, a shorter period of ischemia—slightly less than 1 hour at 37.5 degrees C.—was tolerated than the 2 hour period reported by Hardin and Bogardus and their associates and the 3 hour period reported by Hamilton and coworkers. We believe one of the reasons for this difference is that the capsular blood vessels and ureteral artery were left intact by these investigators. Another factor which prolonged their tolerable ischemic period was the hypothermic effect produced by exposure of the kidney to room air which is lower than body temperature. It is interesting that Hamilton found a greater mortality during the summer, with high environmental temperature, than in the winter.

In the second group of dogs, the kidney temperature was maintained at 37.5 degrees C. for varying periods and the contralateral nephrectomy was delayed for 3 weeks to estimate the reversibility of the kidney damage. As was expected, with this recovery period allowed the remaining kidney, the tolerable period of ischemia was prolonged. Although the curve shown in Figure 3 does not exactly match the previous curve, the similarity is obvious and indicates an increase in the critical limiting temperature time range to between 60 and 75 degree hours.

The reaction to endotoxins of the gram negative bacilli is characterized by pyrexia, shock, diarrhea, and prostration. The reason for the lowered renal tolerance to ischemia in the rabbits given the Shigella endotoxin is undoubtedly complex but in view of the evidence presented by these studies it apparently can be explained by the increased tissue metabolic rate associated with fever.

The limiting effect of increased organ temperature on its ability to tolerate ischemia has been shown in the dog kidney. This finding has important implications in itself and when extended to other organs. Generally speaking, a febrile patient would not be expected to tolerate a hypotensive stress during a surgical procedure as well as would a normothermic individual. With a given period of ischemia a higher incidence of renal failure or neurologic damage presumably would result because of the increased metabolic needs of these organs during fever.

Superior mesenteric artery occlusion treated expectantly has nearly a 100 per cent mortality and even with prompt surgical treatment morbidity and mortality are high because of already gangrenous bowel. Although this surgical emergency is usually accompanied by a normal or subnormal temperature, with mesenteric embolus originating from an active bacterial endocarditis

there may be fever which would be expected to reduce salvage in this situation.

Dissecting abdominal aortic aneurysms are frequently accompanied by fever. In this situation, emergency operation, with occlusion of the blood supply to the lower part of the body for graft placement in all probability would lead to a higher incidence of ischemic changes in the spinal cord and lower extremities and a higher mortality rate than at normal body temperature.

Occlusive arterial disease involving the heart, intestine, brain, and lower extremities eventually reaches a point at which needed oxygen is supplied only at basal metabolic levels. With fever, if not treated promptly, permanent ischemic damage could result because of the relative insufficiency of oxygen at increased tissue temperature.

SUMMARY

It was concluded that there is a reduction in the permissible period of renal ischemia with either local warming of the kidney up to 41 degrees C. or systemic hyperthermia produced with endotoxin. After a contralateral nephrectomy, the critical limiting temperature time range of renal ischemia in dogs appears to be relatively constant at 35 to 40 degree hours, between 5 and 41 degrees C., but can be increased by allowing a 3 week recovery period before the contralateral nephrectomy.

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CANCER OF THE THYROID AND PREVIOUS IRRADIATION

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CANCER OF THE THYROID is frequently regarded as a potential complication of low dose irradiation of the head and neck area in childhood. Of the hundreds of thousands of children in the Chicago area who had radiotherapy to the head, neck, and chest during a period of 10 years, Clark encountered 13 cases diagnosed as thyroid carcinoma. These patients had had small doses of radiotherapy to the thymus, to the neck, or to the tonsil region from 3 to 10 years previously. The estimated dose in the region of the upper margin of the thyroid in the 4 cases of tonsil disease was about 60 roentgens during a period of 2 weeks. In the group with lymphoid hyperplasia of the nasopharynx it was only 18 roentgens to the thyroid region. This dose was formerly often exceeded during simple fluoroscopy of an infant's or child's chest. Therefore, it is reasonable to estimate that many hundreds of thousands of children in the Chicago area had a diagnostic dosage during the years in question to an amount as great as or greater than this therapeutic dosage.

The reported death rate from thyroid cancer has not increased between 1940 and 1958. The reported incidence rate has increased but slightly, by a factor of less than 2. It is therefore to be questioned whether there is any serious connection between such nominal dosage in the thyroid area and subsequent neoplasia in that gland. For example, working in Chicago with clinical material similar to that of Clark, Uhlmann was not able to find any case of thyroid cancer in a follow-up study of 480 of 2,500 children formerly treated for head and neck conditions or for thymic hyperplasia.

Simpson and associates, working in a different area, did report 1 infant to whom the incredible dose of almost 3,000 roentgens was given to the thyroid region in a period of about 1 month. This was obviously excessive and is conceivably related to subsequent neoplasia.

Snegireff, investigating a large series of children irradiated in the thymic area, was able to find no striking increase in thyroid cancer prevalence. In a detailed study of 148 patients who had received irradiation in childhood and infancy because of an enlarged thymus gland not a single malignant neoplasm was encountered. Snegireff concluded: "The previously reported high incidence of primary cancer of the thyroid and of leukemia following irradiation for thymic enlargement is not borne out in our sample."

Latourette and Hodges studied 867 patients who had received thymic irradiation as children. They found no significant increase in neoplasms during the decades studied. They noted 1 case of thyroid cancer as opposed to a normally expected incidence of 0.06.

Conti and Patton reported a group of 1,564 children treated with irradiation in Pittsburgh and studied in 1948. These children had received roentgen-ray therapy to the thymic area, mostly in doses of about 150 roentgens in 6 days. Ninety per cent of the children were contacted again 11 to 18 years after therapy. The names of those not located were searched for in the death records of the Pennsylvania State Department of Health. Four cases of malignant disease were expected to occur in this group, but not one was found. Statistically, 1 case of leukemia was expected; none was

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observed. Conversely, there was no significant difference between the number of expected and observed cases of cancer in general in the untreated siblings.

Many other observers in this difficult field have emphasized the fact that no conclusions can be drawn as to the relationship of the apparently increased incidence of thyroid cancer in some portions of the country and thymic irradiation, because no adequate control series has yet been reported.

TABLE I.—HEAD AND NECK IRRADIATION AND SUBSEQUENT THYROID CANCER AFTER FOLLOWUP PERIODS OF 7 TO 25 YEARS

Authors and year	*No. of patients treated*	*No. of thyroid cancers observed*
Clark 1955	Not stated	13
Simpson et al. 1955	1722	6
Uhlmann 1956	480*	0
Snegireff 1959	148	0
Latourette and Hodges 1959	867	1
Conti and Patton 1948	1564	0
Garland 1960	1780†	1

*2,500 treated, 480 traced.
†Many but not all traced.

PERSONAL EXPERIENCES

During the earlier portion of my more than 30 years in hospital teaching practice and private practice in the San Francisco area, it was not uncommon to employ radiotherapy for patients with benign enlargement of the thymus, for pertussis, and for other conditions now seldom so treated. It was and still is common to irradiate children for lymphoid hyperplasia of the nasopharynx, when this disease is related to tubal deafness which can be a serious disorder and can be relieved or cured by correct irradiation in many cases.

From a review of these hospital and office records made between 1930 and 1940 the following data represent a sample of the average annual number of young patients, mostly under the age of 15 who were treated with radiotherapy to the head and neck area: Hyperplasia of the lymphoid tissue of the nasopharynx, 20; benign enlargement of the thymus, 20; cervical adenopathy, 18; tinea capitis, 15; acne vulgaris, 6; hemangioma, 6; and miscellaneous conditions, including whooping cough, 4. This gives an average annual total of 89 such cases, a conservative figure.

The dose of radiotherapy given to these patients ranged from amounts as low as 50 rads in 1 day to the thymic area to doses as high as 600 rads in 4 weeks to the area of Rosenmuller's fossa. It is estimated that 1,780 children had such treatment. Only 1 case of thyroid cancer is known to have developed in this group.

If, during the years 1925 to 1945 there were 1,000 radiologists in the United States with comparable practices, there might then have been 89 patients so treated, multiplied by 1,000, multiplied by 20, or roughly 1,780,000 children treated during this 20 year period.

During the same time a much larger number of children and infants had fluoroscopic and radiographic examinations of the chest by pediatricians, chest specialists, internists, general practitioners, and radiologists. Many such examinations resulted in thoracic and thyroid area doses within the therapeutic range of 10 to 50 roentgens. It is my estimate that at least 4,000,000 infants and children had such dosage in this country during the two decades in question.

CANCER OF THE THYROID

The reported death rate for cancer of the thyroid in the United States as a whole has been recorded annually since 1939, the first year in which this type of cancer was listed separately by the Bureau of Vital Statistics as a cause of death. A glance at the data published up to 1958 shows that the death rate has remained static, approximately 0.5 per 100,000 per annum.

Some investigators claim that these death rates do not give a true picture of the prevalence of thyroid cancer since so many patients are cured. Others do not quite agree that this disease is so readily curable. At any rate, incidence rates are available

for the state of Connecticut and reveal that during the 20 year period between 1935 and 1955 the reported rate in that state did increase moderately, perhaps by a factor of 2. A portion of this may of course be due to better diagnosis in recent years and to the removal of adenomas showing microscopic cancer. It is quite clear that the incidence rate did not increase proportionately to the enormous increase in the amount of irradiation of the head and neck area during the antecedent period between 1925 and 1945.

It is noteworthy that, although the sex differences in the irradiated population of children is not reportedly different, the sex differential rate in patients with thyroid cancer remains at the usual one of 3 females to 1 male.

It is also noted by many investigators that there is still no adequate control series on record, that is, no series of children diagnosed as having enlarged thymus glands and followed carefully for 10 or more years without radiotherapy (Table I).

SUMMARY

Some investigators have reported an association between low dose head and neck irradiation and subsequent cancer of the thyroid in children and adolescents; other experienced investigators have failed to find such an association.

If there were a significant relationship between low dose irradiation and subsequent neoplasia, the prevalence and death rate from cancer of the thyroid should now be greatly increased in this country. There is a slight increase in reported prevalence in one state, but there is no evidence of any national increase in reported death rates from thyroid cancer.

From 1925 to 1935 there was probably a 50 fold increase in exposure of infants and children to diagnostic and therapeutic irradiation in this country, as compared with earlier decades in this century. Millions of children were so irradiated. From 1939 to date there has been no increase in the age-standardized death rate from thyroid cancer.

An additional series is reported of more than 1,780 patients, mostly infants and children, treated by low-dose irradiation to the head, neck, and upper thoracic area. In this series there has been observed to date only a single case of thyroid cancer.

An etiologic connection between low dose neck area irradiation and subsequent thyroid cancer is not regarded as established.

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THE ENGINEERING DESIGN OF HIP NAILS AND THE DEVELOPMENT OF THE H-BEAM NAIL

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IN THE PAST, much attention has been paid to the metallurgy of implants and very much less to the soundness of their design from an engineering standpoint. Sometimes, there is a tendency to blame failure of the implant on corrosion of the metal alone. Design, however, may play a very important role in the behavior of an implant in the body, particularly when repeated stress is a factor.

The most obvious area in which to investigate the role of design in implant behavior appears to be in fractures of the neck of the femur where many types of devices are used to maintain reduction. Implants used to treat these fractures are subjected to greater stresses than those used in many other parts of the body, as no external splintage is usually used. In addition, the limb beyond the hip provides a long lever arm which magnifies the forces acting on the device. Also, in the interests of his general condition, the patient is often mobilized at a very early date, albeit non-weight bearing, and may be out of bed in a chair the first postoperative day.

THE PROBLEM OF THE HIP NAIL

In general, this study is concerned with hip nails rather than screws and, although screws were tested and considered, this part of the work is incomplete and will not be stressed.

Several things are required of a hip nail if it is to do its job properly. It must be made of an inert or corrosion resistant metal and be prepared in such a way that there are a minimum of defects both on the surface and within the metal. It must be strong and resist stress cracking, fatigue fracture, and stress-corrosion cracking in all planes. These last three types of failure are to some extent interdependent and are to a great degree determined by the metal used and the metallurgical condition of that metal.

The nail must be easily insertable while at the same time doing a minimum of damage to living tissues. A sharp end allows the nail to be hammered in with a minimum of force and thus is less likely to damage the femoral head. The nail should destroy as little of the bone as is compatible with good strength and fixation and should thus have the smallest feasible cross-sectional area. Too large a cross-sectional area would be likely to destroy vital blood vessels and cause avascular necrosis of the femoral head. In this context it should be mentioned that any screw device can easily spin the femoral head upon engaging it across a fracture site and so tear off any remaining periosteum and blood vessels.

The hip nail should grip both femoral head and shaft firmly and resist rotational movement of either fragment. It is desirable that the nail should have little tendency to cut out of the bone and thus should present a relatively flat superior surface to the greatest stresses, especially weight bearing.

The main concern is thus to design a nail with the smallest cross-sectional area yet at the same time having a design which will distribute the stresses adequately and so give great strength. In addition, if shortening of the neck occurs during healing of the fracture, the nail should probably be able to slide out enough to compensate.

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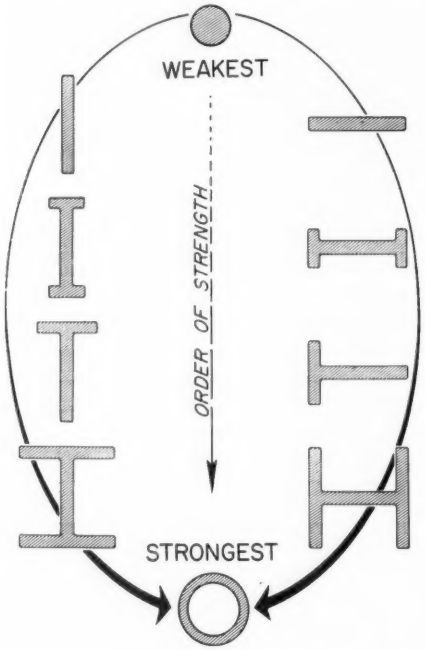

FIG. 1. This diagram shows the effect on strength of a beam obtained by altering its shape while the cross-sectional area remains constant. At the top, the solid rod is the weakest design. A flat bar is stronger only in the upright position but is weaker than the rod when on its side. The I-beam is stronger than the bar in both directions. The H-beam is stronger than the I-beam, especially in the H-position but also in the H-on-the-side position.

In standing and walking, the major axis of stress on a hip nail in situ is obviously from above down. This axis flexes approximately 20 degrees at the center of the femoral head at the beginning of the stance phase and extends approximately 20 degrees at the end of the phase. Thus, in walking, a nail in the femoral neck is never tilted by more than 20 degrees either way around its long axis. In rising from a sitting position, however, the hip is flexed 90 degrees at the start of the movement, and a heavy strain continues until the leg reaches 180 degrees and the patient is standing. The nail is thus stressed first while lying on its side, then finally in the upright position. This type of stress is naturally not as frequently applied as that of walking. In a normal hip joint, torsional strain of the nail during hip motion is minimal, as the joint surfaces have a very small coefficient of friction and the femoral head is not gripped by the acetabulum. In a diseased hip where there is friction between the rough surfaces of the joint, torsional strain may be very great. It would be desirable to know more about the torsional strength of various beam designs.

In view of the many factors involved, there is an obvious need for investigation into the general principles of good design of hip nails. The lessons which are learned may then be applied to the stems of prostheses as well as to intramedullary implants in general.

DESIGN IN RELATION TO STRENGTH

Presuming a suitable corrosion-resistant metal has been selected for the manufacture of an implant, the introduction of some general principles of sound engineering in its design may materially increase its resistance to stress, fatigue, and stress-corrosion cracking. For the purposes of this paper, corrosion will be presumed to accelerate the failure of the device by fracture by attacking the site of the first fatigue failure, or at a notch, or by weakening the implant by surface pitting, according to Ferguson. In order to compare and contrast various designs, the influence of corrosion will thus be considered a common denominator and ignored.

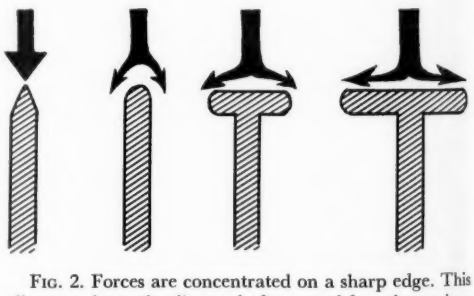

FIG. 2. Forces are concentrated on a sharp edge. This diagram shows the dispersal of an equal force by various edges. The flatter surface gives the smallest local concentration of force.

Bechtol and Murphy have investigated the strengthening of hip nails and have discussed the general principles involved. In general, a solid round rod will be considered the starting point and, therefore, the weakest design (Fig. 1). By using the same cross sectional area of metal but modifying the design, strength may be increased several hundredfold. By flattening the rod out, a bar is obtained. When used as a beam, this is very strong when stressed standing on edge but very weak when tested flat on its side. By widening the edges of the beam to form an I beam, strength is greatly increased in the upright position but only a little in the side position.

The shape of the edge of the beam is very critical (Fig. 2). Stresses are concentrated on sharp edges and lead to early failure in fatigue tests and also in straight loading tests. Rounding off the edges strengthens the design and flattening them out, as in the I beam and H beam, strengthens them even further by distributing the forces over a wider area.

The I beam, however, is very weak when stressed across its broad dimension. If the wide ends are further widened so that there is a flat bar at the edges of the beam, we get the H-beam shape. When stressed in the H-on-the-side position, this design is very strong. It is somewhat less strong in the H position but still materially stronger than the other designs, for one now has two upright beams.

Theoretically, the strongest design is that in which the given mass of metal is furthest removed from the center of the cross section, often referred to as the centroid. The best conditions pertain in the circular or O cross section, and there is great strength in the square O cross section. While this is true, it does not help in the designing of a hip nail, as the O shape would allow free spinning around a nail and the square O would cut off from a blood supply a large amount of bone within the nail. After extensive investigation of the problem and discussion with Mears and his team at United States Steel Research, the H-beam shape appeared the best compromise, giving greatly increased strength in all axes, a good, locking key shape to hold the bone, and the smallest possible cross-sectional area for any required strength.

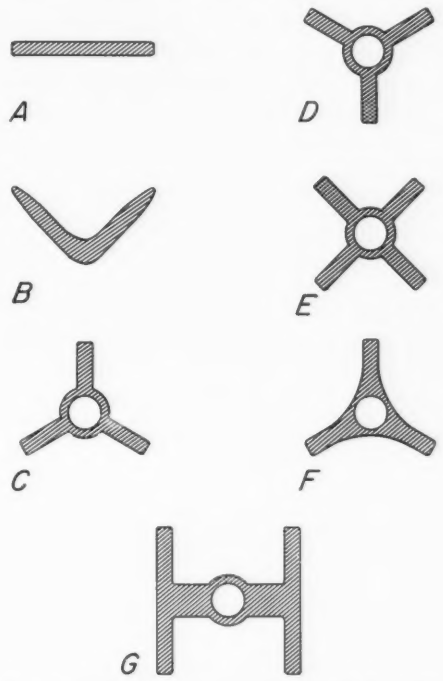

FIG. 3. A diagrammatic presentation of the various cross-sectional shapes of hip nails. The flat blade plate at the top left is the weakest. Working down through the V and then the three and four-flanged nails on the right, we get to the strongest, the H-beam nail.

THE DESIGN OF AVAILABLE HIP NAILS

The screws of various shapes and sizes used to fix femoral neck fractures are all essentially round rod beams. Devices such as the Lorenzo screw would be strong if they did not have to have a thread, for they would then be a cannulated thick rod. Naturally, they would then be useless as fixation devices, for they would not prevent rotation of the head on the neck of the femur. Fracture can occur at the distal end of the thread of any half threaded screw, for there is, in fact, a notch at this point. Screws,

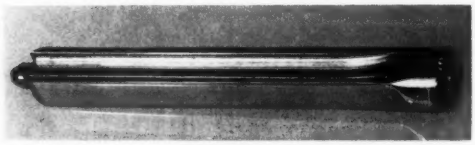

FIG. 4.

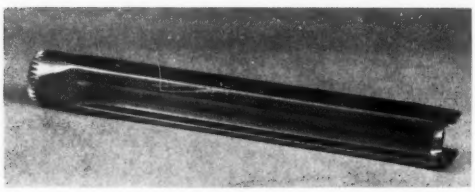

FIG. 5.

FIG. 6.

FIG. 4. Photograph of a stainless steel H-beam nail. Note the chisel-like sharp edge.

FIG. 5. Photograph of a cast vitallium H-beam nail with an osteotome edge.

FIG. 6. Photograph of an early unsuccessful test specimen in which a portion of a screw was clamped between two holders. The test specimens tended to fracture within the holder.

in general, present a weak resistance to fatigue and stress except if they are huge and occupy a great volume of bone. In the course of this investigation, some screws were tested and were easily broken. Further work on this aspect would be desirable.

The blade plate, while not usually used for the fixation of femoral neck fractures, is used for trochanteric fractures (Fig. 3). The flat blade is theoretically very weak when used so that its flat surface is under tension, i.e., uppermost. The blade was modified by Haboush to produce an I beam on the side. This is the weakest aspect of the I beam and the nail was still not ideal. When the flat blade is modified into a V it gains strength, but stress is now concentrated on both apexes of the limbs of the V.

Smith-Petersen and associates designed the trifin nail in 1925 and reported it in 1931. The trifin design was chosen to secure rotation-proof fixation to both femoral head and shaft with a minimum of bone displacement. This nail is strongest when placed with two fins cephalad and the weakest with one limb so oriented. In each case, forces can concentrate on the apexes of the fins. It is better to distribute them over two fins than let them concentrate on one. The trifin nail, since cannulated by Johansson, has been modified to take a larger diameter guide wire and also beefed up by Watson-Jones to eliminate all sharp corners, producing a sort of three-cornered hat cross section. The Watson-Jones nail, though very strong, may leave something to be desired from the point of view of rotational fixation. A four-flanged nail was developed by McLaughlin and is stronger than the trifin types but still takes all the stresses on relatively sharp fins, which is not ideal both from the point of implant strength and that of the nail cutting out superiorly through the bone of the femoral head. The strengths of various designs of

TABLE I.—FATIGUE TEST RESULTS OF TRIFIN SPECIMENS

Sample No.	*Applied load, pounds*	*Induced stress, lbs./in.²*	*Fatigue life, No. of reversed stress cycles**	*Remarks*
1	91	53,900	54,800	Partial fracture
2	81	47,900	68,200	Clean fracture
3	68	40,200	1,806,300	Clean fracture
4	58	34,300	2,483,300	Clean fracture
5	53	31,200	3,635,600	Clean fracture
6	51	30,200	21,005,300†	No failure
7	48	28,400	24,607,000†	No failure
8	38	22,500	33,176,000†	No failure

*Specimens that lasted 10 million cycles were considered successful.
†Specimen was removed from machine at this point.

TABLE II.—FATIGUE TEST RESULTS OF I-BEAM SPECIMENS

Sample No.	*Applied load, pounds*	*Induced stress, lbs./in.²*	*Fatigue life, No. of reversed stress cycles**	*Remarks*
1	91	23,800	118,100	Clean fracture
2	81	21,200	123,500	Clean fracture
3	71	18,600	680,000	Clean fracture
4	68	17,800	8,927,900	Clean fracture
5	58	15,200	13,762,200†	No failure
6	48	12,600	15,342,600†	No failure

*Specimens that lasted 10 million cycles were considered successful.
†Specimen was removed from machine at this point.

nails and nail-plate combinations has been given by Martz.

THE H-BEAM NAIL

The ideal method of testing the strength of a structure is to test the device itself. So, taking into consideration the factors mentioned previously, two cannulated H-beam nails were designed, one of 11 millimeter square and one of 9 millimeter square size (Fig. 4). All corners were rounded and the leading edges sharpened to a chisel edge.

Later on, similar but modified H-beam nails were made of cast vitallium (Fig. 5) and have an osteotome-like edge. All these nails were designed to be used with a Thornton or McLaughlin plate if desired.

TESTING THE STRENGTH OF THE H BEAM

The general question of testing hip appliances has been discussed by Martz, McKeever, and Murphy. The strength of a beam may be tested in at least three ways. One of these methods had to be selected as the main one for the purposes of this experiment.

A transverse bending test may be carried out by supporting one end of the beam and applying a load at a predetermined point out along its length. The load is then increased until the beam starts to bend, the yield point, and is continued until it fractures. This method was used to test cast vitallium H-beam nails and to compare them with three- and four-flanged nails.

Our main interest, however, is in the beam's ability to withstand many interrupted stresses as in walking, in other words, in its fatigue strength. Two ways could have been used to test this aspect. First a vibrating type fatigue testing machine could be used to test the device across first one axis and then another. Such a machine was not available to us. Second, a rotating beam fatigue testing machine of the Moore type could be used. Here the specimen is stressed while rotating, so that each axis is stressed in tension in turn, giving a very severe test of its fatigue resistance. These machines were available. As has been explained previously, torque is probably not too important a factor in the presence of a normal hip joint but is, of course, if the nail is used for arthrodesing a hip or if the hip is ankylosed or stiff. Torque tests would be of value and interest in assessing implants and should be carried out.

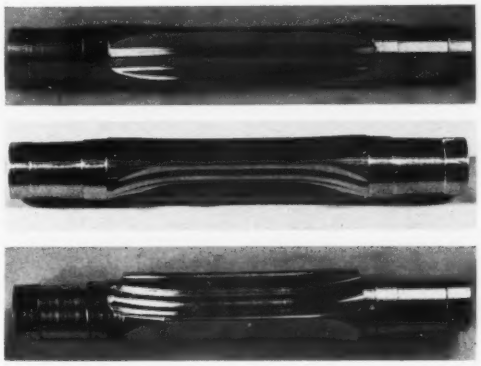

FIG. 7. Photograph of the final test specimens which were each machined out of a solid piece of A.I.S.I. 316 stainless steel. Three types are shown. From above down they are the trifin, I-beam, and H-beam shapes. Further smaller and also slimmer H-beam specimens were also tested.

TABLE III.—FATIGUE TEST RESULTS OF H-BEAM SPECIMENS

Sample No.	*Applied load, pounds*	*Induced stress, lbs./in.²*	*Fatigue life, No. of reversed stress cycles**	*Remarks*
A. Large: Area = 0.1047 in.²				
1	91	16,800	2,087,600	Fractured in holder
2	81	14,900	15,291,900†	No failure
3	68	12,500	17,880,000†	No failure
B. Thin: Area = .0559 in.²				
4	91	—	326,600	Clean fracture
5	81	—	13,966,700	No failure
6	68	—	14,253,000	No failure
7	68	—	3,512,000	Failed in taper
C. Small: Area = approximately .0560 in.²				
8	81	—	415,400	Clean fracture
9	68	—	10,089,400	No failure
10	68	—	5,389,200	Failed at end

*Specimens that lasted 10 million cycles were considered successful.
†Specimen was removed from machine at this point.

TABLE IV.—FATIGUE TEST RESULTS

	Load to 10^6 cycles, lbs.	*Cross section area, in.²*
Trifin	51	.0524
I-beam	58	.0825
H-beam	81	.1047
Thin H-beam	68	.0559
Small H-beam	81	.0560 (approx.)

a

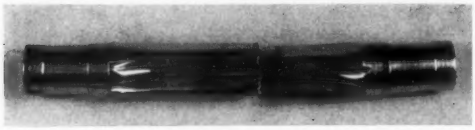

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FIG. 8.

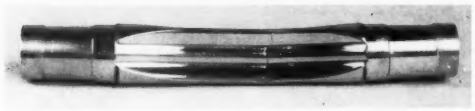


FIG. 9.

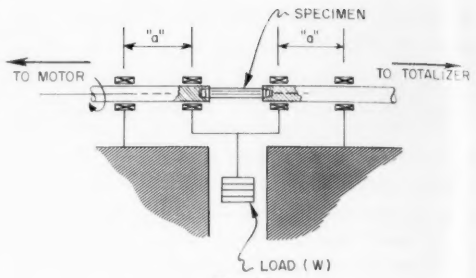


FIG. 10.

FIG. 8. Photograph of, a, a failed trifin and, b, a failed I-beam specimen.

FIG. 9. Photograph of specimen No. 1. In this test, the machine stopped before complete fracture. The crack can be seen originating from the apex of one fin.

FIG. 10. Diagram of the Moore machine. The specimen is in the middle and the fulcrums are at each end of the supporting beams. The weights are hung from the holders between the fulcrums and the specimen.

TESTING METHOD

Because it was available and because it seemed very suitable for our purposes, the Moore rotating beam fatigue testing machine was selected.

The development of suitable test specimens took much time and thought. Great difficulty was experienced in fixing an entire hip nail or screw at either end so that it could be inserted into the testing machine with enough security to eliminate rocking and thus to avoid fracture at the holding jaws (Fig. 6). Special testing specimens were, therefore, designed with the central 1 inch exactly reproducing the nail design (Fig. 7), and the ends machined to fit the holders of the Moore machine. These specimens were each made from a single piece of A.I.S.I. 316[1] stainless steel and were prepared in every way exactly as are surgical nails with highly polished surfaces.

The Moore testing machine (Fig. 10) rotates the test specimen while a constant stress is applied through a selected weight suspended from the specimen holders. The distance "a" between the fulcra at either end and the point of weight suspension was 4 inches in this case. The under surface of the specimen is thus under tension, i.e., distraction, and the upper surface is under compression. The machine may be run until the specimen fails, when it automatically stops. At one end of the rotating holders is the motor and at the other a totalizer which records the number of cycles. The weight of 91 pounds was used as the first test and if failure occurred it was reduced to 81 pounds for the second specimen and so on until the specimens could not be broken. If the specimen withstood 10 million reversed stress cycles, the endurance limit, it was found that failure did not occur up to 24 to 33 million cycles. This was true for stainless steel only. One vitallium screw specimen failed at 17 million cycles. The experiments with screws were not, however, strictly comparable and are incomplete.

Test specimens were prepared with a trifin, an I-beam, and three H-beam designs. The first H-beam design had a greater cross-sectional area than either the trifin or the I beam, so a small H beam and a thin H beam, both with almost the same cross-sectional area as the trifin specimen, were prepared.

The early tests with eight trifin and six I-beam specimens were carried out by

[1]The letters A.I.S.I. stand for American Iron and Steel Institute. The numbers 316 classify the metal according to metallurgical practice.

O'Donnell in the Metallurgical Department of Engineering at the University of Pittsburgh. The H-beam specimens were tested by Moore testing machines.

THEORETIC CONSIDERATIONS

Before detailing the results of the experiments, the theoretical considerations underlying the work will be discussed. In general, it may be stated that the stress induced by a load is given by the following formula:

$$(1)\quad S=\frac{M}{Z}$$

In which

S = Induced stress (lbs. per in.^{2})
M = Maximum bending moment caused by the load (in.-lbs.)
Z = Section modulus of the part resisting the action of the load (in.^{3})

The maximum bending moment (M) is determined by the manner in which the part being tested is loaded. In this case, the part is loaded similarly to a revolving beam, fixed on both ends with a concentrated load at the middle.

For the Moore type of loading:

$$(2)\quad M=\frac{Wa}{2}$$

In which

W = The weight applied to specimen measured in pounds.
a = The distance from the reaction point to the loading point measured in inches (Fig. 8)

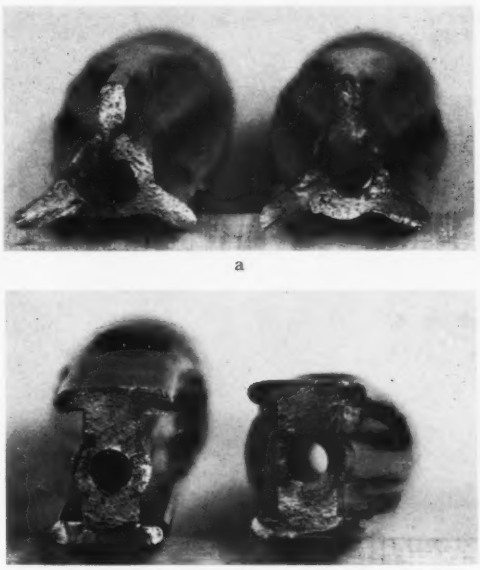
In this case, a = 4 inches

Therefore: $(3)\quad M=\frac{4W}{2}=2W$ in. lb.

The section modulus may be considered as a mathematical symbol that takes into account the design of the part. The section modulus is the product of the various areas comprising the cross section of the part times the distance that each individual area is from the theoretic center of the cross section or centroid.

For any type of beam:

$$(4)\quad Z=\frac{I}{Y}$$



a

b

FIG. 11. Photograph of the fractured ends of two specimens showing typical fatigue failures. Metallurgical sections were prepared of many of the specimens and confirmed this appearance. a, Trifin specimen, and b, I-beam specimen.

In which

Z = Section modulus measured in in.^{3}
I = Moment of inertia, dependent upon the cross section of the specimen and equal to the sum of the products of the component areas times the square of their distance from the axis of the specimen, measured in inches^4.
Y = Distance from the neutral axis of the specimen to the outermost fibers or metal part, measured in inches.

Combining formulas 1, 3, and 4, we have

$$(5)\quad S=\frac{2W}{\frac{I}{Y}}=\frac{2WY}{I}\ \text{lb. per in.}^2$$

Since $\frac{2Y}{I}$ is a constant, C, determined by the cross section of the specimen, we have

$$(6)\quad S=WC$$

The stress in the specimen is thus directly proportional to the applied load.

It may thus be seen from the formula 1 that the stress, S, induced by any given load, as determined by the moment, M, will be

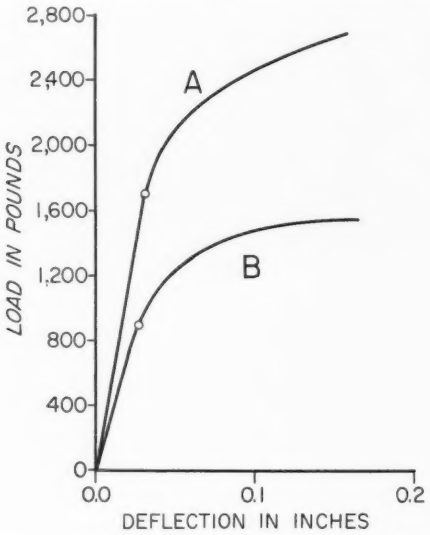


FIG. 12. Diagram of the horizontal loading tests carried out on cast vitallium H-beam nails with a 2½ inch beam, *A*, in the H-on-the-side position and *B*, in the H position. The yield point is marked by a circle on each curve. In both directions, they seemed substantially stronger than three or four flanged designs.

reduced if the section modulus, Z, is increased. Or, in simpler terms, by increasing the section modulus of the metal splint, we allow the splint to carry a greater load without increasing the stress induced by the increased load.

Calculations of the section moduli of the three types of splints tested show that for the Smith-Petersen type splint, Z = .00427 cubic inch; for the I-beam type, Z = .00768 cubic inch; and for the thick H-beam type, Z = .0137 cubic inch.

RESULTS

Of twenty-five one-piece test specimens, three failed at points other than the middle 1 inch or test zone, usually at the ends which were specially shaped for the Moore holders. The results of the tests are detailed in Tables I, II, and III, summarized in Table IV. Failure was in all cases by a clean fracture, usually somewhere near the midpoint of the specimen (Fig. 8). The original H-beam nail, however, could not be fractured and after prolonged testing the machine failed.

The fracture in a trifin nail apparently may start at the apex of a fin as would be expected, as this is the point of stress concentration. This was shown in the first specimen which was recovered before a complete fracture had occurred (Fig. 9). The appearance of all fractures in the test area was similar and were typical of fatigue type failures (Fig. 11).

In addition to the fatigue tests, transverse bending tests were conducted on cast vitallium H-beam nails (Fig. 12). The nail loaded in the I position, showed a yield strength of 1,700 pounds with a deflection at yield of .031 inch, and an ultimate load of 2,688 pounds with a deflection of .159 inch. The nail failed by fracture. Loaded in the H position, the yield was 900 pounds with a .027 inch deflection, and ultimate load was 1,640 pounds with a .165 inch deflection. It also failed by fracture. These tests were made with a 2½ inch span, i.e., 2½ inches between fulcrum and the point of application of force.

Comparable tests were made with 3-flanged and 4-flanged vitallium nails but across a 4 inch span. Mathematical calculations were made to correlate these data to a 2½ inch span. The 4-flanged nail demonstrated a calculated yield of 535 pounds and the 3-flanged nail a yield of 425 pounds.

DISCUSSION

Within the limits of the fatigue tests used, the H-beam seems to have a greater fatigue strength than either the trifin or I-beam designs. Although an increase in cross-sectional area makes the H beam even stronger, it appears from the tests of those with an essentially comparable size to the trifin, that design itself has contributed to their superior performance. The transverse-bend tests on the vitallium models, while inconclusive, also tend to confirm these findings. The force necessary to fracture the H-beam nail is of the same order as that required to

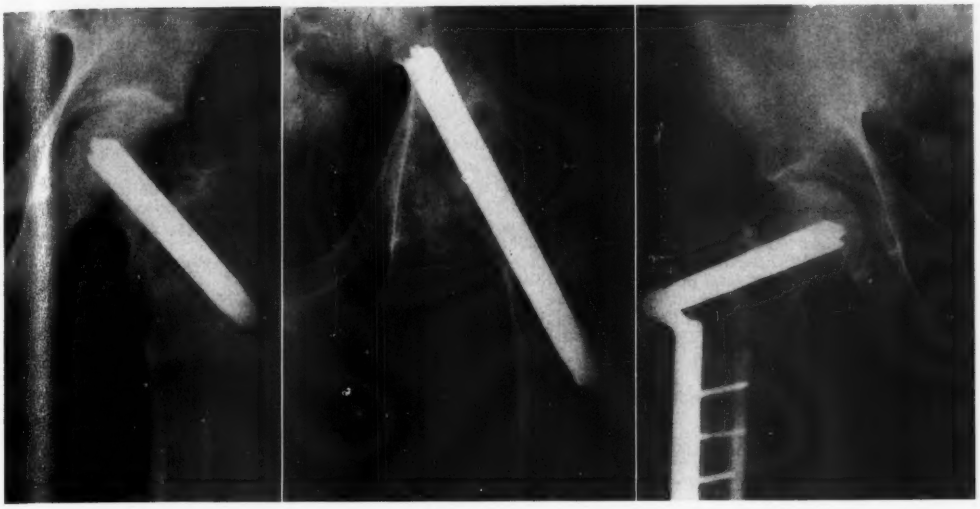


FIG. 13. FIG. 14. FIG. 15.

FIG. 13. Roentgenogram of a fractured neck of femur fixed with an H-beam nail.
FIG. 14. Roentgenogram of an arthrodesis of the hip using a long H-beam nail.
FIG. 15. Roentgenogram of a pertrochanteric fracture of the femur fixed with an H-beam nail and a plate and screws.

fracture the femoral neck, which, according to Smith, is about 2,000 pounds.

Naturally, it is realized that the only true test of a device must be one carried out in the field, i.e., with the nail in place in the body. Only then can the full significance of corrosion be apparent as an accelerator of failure and only then will the true forces be operative.

Good design which spreads stresses over a wide area and which avoids notching and other weakening faults will probably also lessen the tendency to stress-corrosion cracking. It is believed that the H-beam design meets these requirements.

The flat superior surface of the H-beam nail not only provides a wide area to dissipate forces but also is an insurance against cutting out of the nail superiorly through the femoral head.

It appears on both theoretical and practical grounds that the H-beam design is an excellent approach to the ideal nail which is equally strong in all directions and that it could be applied to the stems of femoral head prostheses and to all intramedullary nails with advantage.

CLINICAL USE

The technique of inserting the H-beam nails is exactly the same as that used for all other cannulated nails. It is relatively simple to insert as the sharp leading edges cut the bone easily. Care must be taken to start the nail through the lateral cortex of the femur via an adequate window if the cortex is very hard, but this problem of starting a nail properly is common to all shapes. To obtain the best results, one of the flat surfaces is placed superiorly or cephalad and the lower one slides up the lower part of the femoral neck like a sled.

A firm hold is obtained on both fragments in femoral neck fractures (Fig. 13) and in arthrodeses of the hip (Fig. 14). In trochanteric type fractures, a plate may be added and secured by a conventional and a reverse threaded screw (Fig. 15). In the case of the vitallium nails, they are also made to receive a McLaughlin plate with a

nylon lock nut. These nails have been utilized satisfactorily in more than 40 cases by several surgeons during the past 3 year period.

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THE USE OF MODIFIED EXPOSURE IN THE MANAGEMENT OF BURN WOUNDS

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THE MANAGEMENT of the burn wound by exposure has probably been employed for centuries. However, it was not recorded in the medical literature until 1887, when Copeland described his method. Since that time, the exposure technique, including such modifications as the application of tannic acid, gentian violet, paraffin, or aluminum dust, has had cyclic periods of favor and disfavor. Generally, the closed or dressing technique was more commonly utilized until 1949, when Wallace (4, 5) of Edinburgh reintroduced the exposure method of local care, first in the management of burns of the face and neck and then in the management of burns of various regions of the body. Pulaski and Blocker were among those who were instrumental in reintroducing this method to the United States. Since 1950, several burn centers in this country have adopted the exposure method as routine in the management of large burn wounds.

At the United States Army Surgical Research Unit in the past 3 years, we have come to rely upon the exposure method in all burn injuries except in some full thickness burns of the hands. In third degree burns, exposure results in the formation of an eschar in 48 to 72 hours, which may serve as a barrier to bacterial contamination until its separation begins within 10 to 18 days post burn. Treatment by the exposure method was usually terminated when the eschar became separated, and the granulating wound was covered with a bulky, occlusive dressing. Observations on many burned patients led to the belief that the application of an occlusive dressing at this time encouraged bacterial growth, increased the metabolic rate, elevated the body temperature, and otherwise interfered with the surface heat loss mechanism. In addition, the patient experienced increased discomfort. Dressing changes, required every 3 to 5 days, necessitated preoperative and postoperative restriction of oral intake and the administration of an analgesic and/or a general anesthetic. If dressings covered the thorax or abdomen, a definite restriction of respiratory excursion occurred. Uninjured skin surrounding the burned surfaces often became macerated and vulnerable to infection, and hemorrhage occasionally occurred unnoticed beneath the dressing. The application of bulky dressings to newly grafted wounds not only had the preceding disadvantages but also precluded direct observation of the skin grafts in the early postgrafting phase when split thickness skin can be lost because of graft displacement, hematoma, serum accumulation, or infection. Donor sites adjacent to grafted wounds cannot be exposed and frequently become contaminated with organisms from wounds covered by a dressing common to both.

Surgeons in some clinics have eliminated the use of bulky, occlusive dressings during skin grafting of certain areas by utilizing an exposure technique during this procedure. The difficulties encountered in utilizing

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FIG. 1. Grafts and a dressing of coarse mesh paraffinized gauze were applied to the right leg, 31 days post burn. The graft take was excellent. The left leg was not ready for grafting at this time, and the granulations are covered with 1 layer of fine mesh gauze.

true exposure technique, that is without any dressings, in grafting extensive burned areas include the following: (1) Grafts are easily dislodged from the granulating surface. (2) Grafting is restricted to the dorsal or ventral surface, while both areas may be ready for grafting. (3) The patient must be immobile for 4 or 5 days after grafting to prevent graft slippage. This causes patient discomfort and may injure dependent granulations. (4) Portions of the grafts laid upon areas of motion may become displaced.

We believed that it would be desirable to develop a method of management which would retain the advantages of the true exposure technique, as well as those associated with the application of dressings and yet avoid the major undesirable aspects of each. A method to accomplish these aims was evolved at this Unit, and for lack of a better nomenclature it has been called "modified exposure."

TECHNIQUE

The procedures utilized in modified exposure are simple and do not require special equipment or skill.

1. Exposure is utilized in the early post-burn phase, and methods of resuscitation remain unchanged from the usual ones.

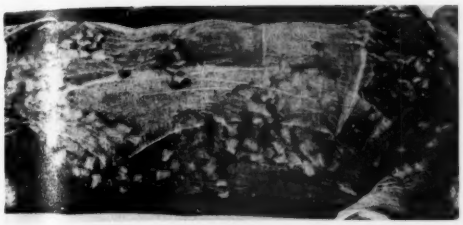
2. The eschar is permitted to remain in place as long as it is unbroken and intact. If there is indication of infection under or on the periphery of the eschar, its removal is begun as a ward procedure. The areas are washed with a surgical detergent, rinsed thoroughly, and débrided. Frequently changed sterile wet dressings may be used on areas with separating eschar to hasten its removal. By this conservative approach to eschar removal, the body is able to set up a defensive barrier of granulations to surface bacteria, and the bacteremia frequently associated with vigorous débridement is minimized.

3. As the eschar is removed and the granulations become exposed, the area is covered with 1 layer of moistened, fine mesh gauze, which is replaced daily. The removal of the fine mesh gauze is facilitated by the application of wet soaks. When the granulations have matured and are ready for grafting, a large, bulky, dry dressing may be applied for 24 hours before operation.

4. The skin for grafting is taken in the usual manner and for ease in handling is spread on 1 layer of fine mesh gauze which has been very lightly impregnated with petrolatum. The graft may be used either as postage stamps or as sheets, depending upon the site of application and the judgment of the operator.

5. The granulating recipient area is thoroughly cleansed and rinsed prior to application of the graft. The fine mesh gauze backing on the graft is removed when the graft is applied. No sutures are utilized.

6. Instead of applying the usual large, bulky, immobilizing dressing at this time,



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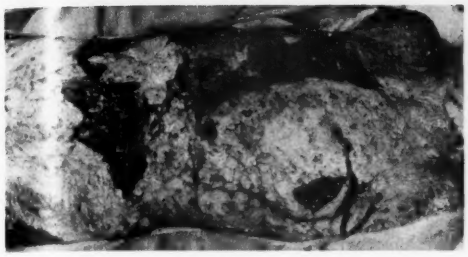

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FIG. 2. a, Postage stamp autografts and/or homografts are held by the coarse mesh gauze dressing, 32 days post burn. b, The graft take is good, 36 days post burn. Additional areas are ready to be grafted. Some eschar remains adherent. c, Skin coverage and survival have been accomplished, 6 months post burn.

a coarse mesh gauze impregnated with paraffin is used. This coarse mesh gauze, with interstices which measure just under one-eighth of an inch in diameter, is cold-sterilized prior to application. A single layer of the paraffinized gauze is placed over the grafts and sutured securely to the tissue around the grafted area with nonabsorbable sutures. The sutures are sparsely placed around the periphery and within the grafted area in such a manner that the gauze will contour to the surface. No dressing other than this 1 layer of coarse mesh paraffinized gauze is applied. The small amount of serum oozing from between the sheet grafts or the granulating areas between postage stamp grafts will permeate the gauze and form a thin, adherent crust. This will further immobilize the grafts and dressings to prevent slippage. The entire area of the graft remains dry and clean for days or weeks after the application of the paraffinized gauze. Circumferential dressings of paraffinized gauze on the extremities may be held by suturing the ends of the gauze together (Fig. 1). Should the dressing become loose postoperatively, it can be tightened by overfolding the gauze and suturing upon itself. Coarse mesh gauze has been left in place for as long as 16 days without local reaction; however, it is our usual practice to remove it in 7 to 10 days postgrafting. It is easily removed by applying soaks to soften the crusts, after which it separates without difficulty.

7. In the extensively burned patient, we frequently have been confronted with areas which are ready for grafting, while in adjacent areas the eschar remains in place. With the use of modified exposure, the areas which are ready with mature granulations can be grafted and the adjacent areas with the eschar may be treated independently. By grafting in this piecemeal fashion, procedures to cover large areas usually can be avoided, grafting can be started earlier, and the wound becomes progressively smaller (Fig. 2a, b, and c).

RESULTS

Modified exposure has been used in 155 skin grafting procedures on 55 patients at

a

b

c

FIG. 3. a, Granulations prior to grafting after burn of buttocks and perianal region. b, Autografts are held securely by the dressing. c, Appearance of burned area after coverage has been accomplished.

the Surgical Research Unit during the past 2 years. Based upon the evaluation of this clinical material, the following advantages were apparent: (1) There was less slippage of grafts under all circumstances; therefore, graft loss was minimized. (2) The grafted areas were visible at all times, and any serum, hematoma, or area of infection was dealt with promptly. (3) It was applicable to all areas and facilitated the management of skin grafts in areas normally considered difficult to graft. This was particularly true in the perineal and anal regions in which the coarse mesh gauze was sutured to the anal margin, effectively protecting the graft from fecal flow and contamination. The anal margin and buttocks could be cleaned after a bowel movement with less fear of graft loss, which so commonly occurs with the bulky, occlusive dressings. As a consequence, it was not necessary to suppress bowel function postoperatively (Fig. 3a, b, and c). Amputation stumps which have always been difficult to manage were easily covered by this method. Areas of motion such as the chest and abdomen were not completely immobilized, and a good graft take was obtained (Fig. 4a, b, and c). (4) Hyperpyrexia, which frequently accompanies the use of the massive, occlusive type dressings, was rarely seen with the modified exposure technique. (5) The dressings were not restrictive and did not complicate the postoperative course by inhibiting respiratory motion or by compressing the abdomen. (6) This procedure allowed piecemeal grafting in extensive burns by permitting the grafting of areas adjacent to intact eschar. This method allowed for earlier coverage, and extensive grafting was replaced by frequent small grafting procedures. (7) This

a

b

c

FIG. 4. a, Wound at the time of grafting, 24 days post burn. b, Coarse mesh paraffinized gauze is applied over sheet autografts. c, Skin coverage accomplished with 1 grafting procedure, 44 days post burn.

technique eliminated the necessity for the redressing of grafted areas at frequent intervals. Prior to the use of the coarse mesh gauze, burns were covered with a bulky dressing, which was removed in the operating room every 3 to 4 days, usually under anesthesia. In such instances, the patient was not only required to be placed on a preoperative fasting period, but, also, received no nutritional intake during the operative procedure and for 2 to 4 hours thereafter. After modified exposure was utilized, the patient was taken to the operating room for the purpose of grafting only. After operation, the coarse mesh gauze was left in place, usually until the next grafting procedure. As was stated previously, these dressings have been left in place for as long as 16 days without local reaction. If one wishes to remove the paraffinized gauze earlier than the next operative procedure, this may be done on the ward after wet soaks or submersion in a Hubbard tank with very little discomfort to the patient. (8) This procedure permitted donor sites which were adjacent to grafted areas to be exposed. This would not have been possible if massive dressings had been applied. (9) The cost of therapy was less. In the treatment of burns, a large number of dressings, composed of numerous layers, increases the cost of the therapy, whereas the paraffinized gauze is relatively inexpensive. (10) In the event of a mass casualty situation, it would be feasible that numerous patients could be treated by a small volume of dressings.

The only disadvantages which have become evident with the use of this procedure are: (1) On occasion, the dressing would tend to become loose due to a decrease in edema. This is not of great consequence, however, since it is easily tightened by overfolding the coarse mesh gauze and suturing to itself. (2) It takes somewhat longer to apply this type of dressing than the conventional massive type, but the time saved by the elimination of suturing the grafts more than compensates for this factor. (3) The coarse mesh gauze is produced only in 6 inch widths, whereas a wider width is frequently desirable. This is obtained by cutting the 6 inch roll into sections and having them sewn together on a sewing machine prior to performance of the operation.

SUMMARY

The personnel of this Unit are convinced that the exposure method in the management of burn injury is more desirable than is the use of massive, occlusive dressings. In order to eliminate the occlusive dressings, even in the grafting phase, the technique which we have called "modified exposure" for grafting has been developed. This is the application of 1 layer of coarse mesh paraffinized gauze over the grafted areas; no other dressing is applied. In our experience, this method has proved extremely useful, and we believe it to be far superior to the conventional bulky dressing technique. Although it is impossible to say that this procedure has reduced mortality or serious infection, it is our opinion that it has contributed materially to the survival of a number of extensively burned patients.

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INTUSSUSCEPTION AS A POSTOPERATIVE COMPLICATION IN PEDIATRIC SURGERY

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INTUSSUSCEPTION has occurred during the early postoperative state after laparotomy in 9 infants and small children during the period 1941 to 1960 at the Los Angeles Childrens Hospital. Three of these were acute postoperative recurrences of intussusceptions previously surgically reduced. Six developed subsequent to abdominal procedures for superficially unrelated conditions.

Such intussusceptions are distinct with regard to the difficulty of accurate preoperative diagnosis. They have not been generally recognized as the unique intra-abdominal postoperative complications of this age group.

CLINICAL SERIES

The basic data concerning the 6 patients in whom intussusception occurred after apparently unrelated operation are found in Table I. Four were infants and all were less than 6 years of age. Three were males and 3 were females. The initial clinical diagnoses were: Meckel's diverticulum in 2, hypertrophic pyloric stenosis in 1, adrenal hyperplasia in 1, mesenteric adenitis in 1 and exstrophy of the urinary bladder in 1.

The two patients with diagnoses of Meckel's diverticulum, Cases 1 and 2, had sudden, massive, gastrointestinal hemorrhages. Hemoglobin on admission was 7.9 and 7.6 grams per cent, respectively. The medical history prior to this episode was unremarkable in both instances. There were no physical findings of note except those which were secondary to anemia. Both patients were explored with a tentative diagnosis of Meckel's diverticulum with ulceration and hemorrhage.

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Laparotomy confirmed this diagnosis and the diverticula were excised. Ectopic gastric mucosa in the diverticulum with associated ileal ulceration was noted upon microscopic study in each case. Both were thus rather typical examples of hemorrhage associated with a Meckel's diverticulum in infancy.

A third child, Case 6, was also found at operation to have a Meckel's diverticulum without apparent inflammation or hemorrhage. The preadmission history in this case, however, was one of 5 days of malaise and abdominal pain localizing in the right lower quadrant. The physical findings in this instance were suggestive of either mesenteric adenitis or acute appendicitis without rupture. At exploration, a diagnosis of mesenteric adenitis was made and an incidental appendectomy and diverticulectomy were performed. Neither organ showed evidence of inflammation upon microscopic examination.

The three diverticulectomies were unusual only in that the ileal closure was made in at least two layers, and in two instances in three layers with internal absorbable and external nonabsorbable sutures.

An 8 week old male infant, Case 3, was admitted with a history of progressive non-bile-stained vomiting of feedings for 3 weeks and weight loss. A right subcostal "tumor" was palpable, and a diagnosis of hypertrophic pyloric stenosis was entertained. This was confirmed at laparotomy and a Ramstedt pyloromyotomy was uneventfully performed.

Case 4 was that of a boy of 4 years in whom a diagnosis of adrenal hyperplasia had been suggested by the development of pubic hair and penile enlargement. An elevated urinary 17-ketosteroid excretion was

TABLE I.—INTUSSUSCEPTION AFTER ABDOMINAL SURGICAL PROCEDURES IN INFANTS AND CHILDREN

Case No. *Sex* *Age*	*Initial diagnosis*	*Initial operation*	*Interval prior to second operation, days*	*Symptoms during interval*	*Suction therapy, duration*	*Type of intussusception*	*Secondary operation for intussusception*	*Result and period of observation*
1 M 23 mos.	Meckel's diverticulum with massive hemorrhage	Excision of Meckel's diverticulum	5	Abdomintention and vomiting, 3 days	Gastric suction, 48 hours	Ileoileal	Laparotomy, manual reduction	Recovery 2 yrs.
2 F 2 mos.	Meckel's diverticulum with massive hemorrhage	Excision of Meckel's diverticulum	25	Intermittent vomiting throughout interval, diarrhea for 2 days	Attempt to pass long intestinal tube, 12 hours	Ileoileal, healed in situ	Ileal resection, exteriorization	Recovery 1½ yrs.
3 M 2 mos.	Hypertrophic pyloric stenosis	Pyloromyotomy, Ramstedt procedure	10	Intermittent vomiting, 10 days, diarrhea and abdominal distention, 3 days	Gastric suction, 30 hours	Ileoileal	Laparotomy, manual reduction, lysis of adhesions	Recovery 8 yrs.
4 M 4 yrs.	Adrenal hyperplasia, bilateral	Laparotomy and bilateral adrenal exploration	11	Abdominal pain and vomiting, 3 days, distention, 1 day	Long intestinal tube passed, 24 hours	Jejunojejunal	Laparotomy, manual reduction	Recovery 4 yrs.
5 F 17 mos.	Exstrophy of the bladder	Cystoplasty using isolated sigmoid segment	26, same hospitalization	Apparently prolonged postop. ileus followed by improvement, followed by vomiting, 4 days	Gastric suction, 72 hours	Ileocolic	Laparotomy, manual reduction	Recovery 3 yrs.
6 F 5 yrs.	Mesenteric adenitis or appendicitis	Meckel's diverticulectomy and appendectomy	5	Improving for 3 days; abdominal pain, vomiting, and rectal bleeding, 2 days	Gastric and long intestinal tube, 48 hours	Ileoileal	Laparotomy, manual reduction	Recovery 2 mos.

demonstrated. The operative procedure consisted of a transabdominal exposure of the adrenal area bilaterally with biopsy of the left gland. No abdominal abnormalities were encountered, nor did excessive hemorrhage or other complications occur.

In Case 5, that of a 17 month old girl, major congenital anomalies had been noted since birth, including vesical exstrophy, a bifid genital tract, congenital hip dislocations, and pelvic kidneys. This patient was subjected to an unusual procedure including isolation of a segment of sigmoid colon used to enlarge the bladder wall posteriorly. Anterior cystoplasty was then performed.

No particular trauma to the small intestine was noted in either of the latter two procedures, Cases 4 or 5, although both entailed rather prolonged air exposure of the intestine because of the duration.

ANALYSIS OF THE INTERVAL BETWEEN THE INITIAL OPERATIVE PROCEDURE AND DEVELOPMENT OF INTUSSUSCEPTION

Demonstration of the secondary intussusceptions followed the initial procedure in 5 to 26 days (Table I), although the time of actual occurrence of intussusception was obviously much earlier in some, as in Case 2. Three patients were not discharged from the

hospital during this interval. The 3 others were at home for 1, 2, and 19 days, respectively. The following data are drawn from observations both at home and in the hospital. Only one significant postoperative complication was observed in this group, with the exception of intussusception. It was prolonged paralytic ileus noted in the patient with exstrophy in Case 5, lasting for 10 days after the colon resection and apparently adequately managed by gastric suction.

In all of the other cases, and in this one after the initial 10 days, the beginning of a return to normal gastrointestinal function was observed, followed by a return of the symptoms and signs of intestinal malfunction. Vomiting was noted in all, and continued, except when interrupted by suction, for 2 to 12 days prior to the second laparotomy. Rectal bleeding was noted in 1 patient, although insufficient to lower the hemoglobin determination. In a second patient, a streak of red blood was noted on a single stool specimen. Acute nonbloody diarrhea was observed in 2 infants prior to the secondary intussusception. Abdominal pain was not prominent in these histories and had no pattern of periodicity.

All patients showed abdominal distention for 2 to 5 days prior to exploration, and a "ladder" pattern was noted in 2. Palpation of the abdomen was negative with respect to the presence of a mass or even a suspected mass in all cases.

As these patients were under study in a medical center during the greater part of or the entire period of the development of intussusception, they all had multiple determinations of serum concentrations and other laboratory tests which are rarely made in cases of intussusception developing under usual circumstances.

Alteration in serum electrolyte concentration reflected principally the severity of vomiting and the effectiveness of intravenous replacement. All patients had initial hypochloremia, 85 to 98 milliequivalents per liter, relatively normal serum potassium levels, and serum carbon dioxide determinations which varied greatly, from 14 to 26 milliequivalents per liter. Subsequent determinations demonstrated the return of these concentrations to normal values during therapy.

A rapidly rising leukocyte count to heights of 17,500 to 30,100 per cubic millimeter was observed during the interval period in 5 cases but was absent in Case 1 in which the count was 8,300 per cubic millimeter. In 3 cases, including the latter, nonsegmented granulocytes accounted for more than 50 per cent of the peripheral leukocytes observed. A granulocytic preponderance was common to all. No significant anemia was noted in any of these patients.

Repeated abdominal roentgenographic studies were the rule, only 1 patient having a single examination. The character of these films is shown in Figures 1 and 2. In retrospect, and usually at the time, they were believed to demonstrate mechanical small intestinal obstruction. Several suggested the presence of moderate amounts of free intra-abdominal fluid. Air was present within the peritoneal cavity in several, and the presence of perforation and peritonitis was suggested incorrectly in one. The majority of these studies, however, presented the familiar diagnostic differentiation between adynamic ileus and mechanical obstruction, with prevailing evidence in favor of the latter.

THERAPY AND THE SECOND OPERATIVE PROCEDURE

Treatment by intestinal suction was employed in all patients. The duration of this attempt was 12, 24, 30, 48 in 2, and 72 hours, respectively. A double lumen tube was passed into the jejunum in 3 cases, although never successfully advanced to or near the site of obstruction by intussusception. Simple gastric suction was employed in the remaining cases.

In 5 cases the preoperative diagnosis was intestinal obstruction secondary to postoperative adhesions. Adynamic ileus, on the

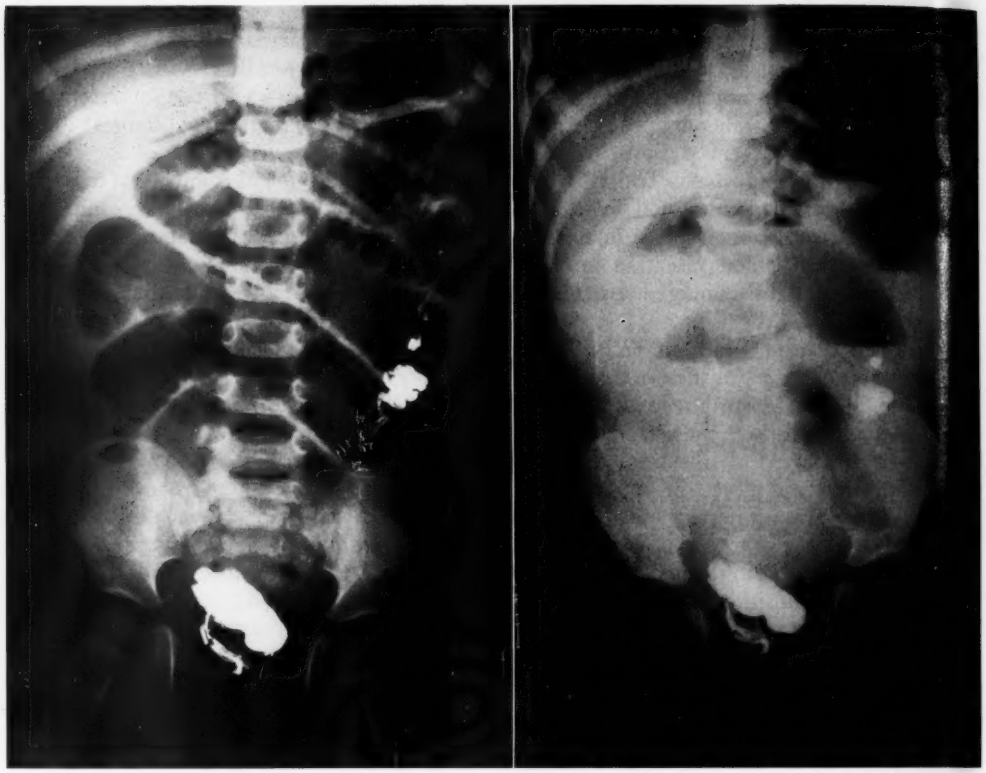

FIG. 1. Supine and erect abdominal roentgenograms of the 23 month old male in Case 1 taken 5 days after a Meckel's diverticulectomy for massive gastrointestinal hemorrhage. Intestinal function had apparently improved progressively for 48 hours after laparotomy and then deteriorated for the same period. The infant had been maintained on gastric and later upper intestinal suction for 2 days. Peristaltic sounds were diminished. At laparotomy an ileoileal intussusception was demonstrated.

other hand, was the working diagnosis in Cases 1 and 5 until shortly prior to the second laparotomy. In 1, Case 6, the probability of intussusception was recognized, but only after hematochezia was noted.

An unequivocal intussusception was found in each case at the second procedure. Five of these were confined to the small intestine, 4 to the ileum, and 1 to the jejunum. The sixth was of the ileocolic variety. The areas of enteric intussusception were 6, 7, 8, 30, and 36 centimeters in length prior to reduction or resection. The ileocolic intussusception had progressed to the region of the splenic flexure. In the 3 cases in which there was a previous ileal incision, a Meckel's diverticulectomy, the intussusception lay entirely distal to the point of the suture line in 1, included the point of closure in another, and appeared to be "led" by the invaginated anastomosis in the third.

The operative findings in Case 2 were those of a viable, partially obstructing intussusception in which the serosa of the intussuscipiens had fused externally with the serosa of the proximal ileum. Its development thus must have occurred much earlier in the postoperative course. At operation it grossly resembled a small intestinal tumor but on section was made up of the six intes-

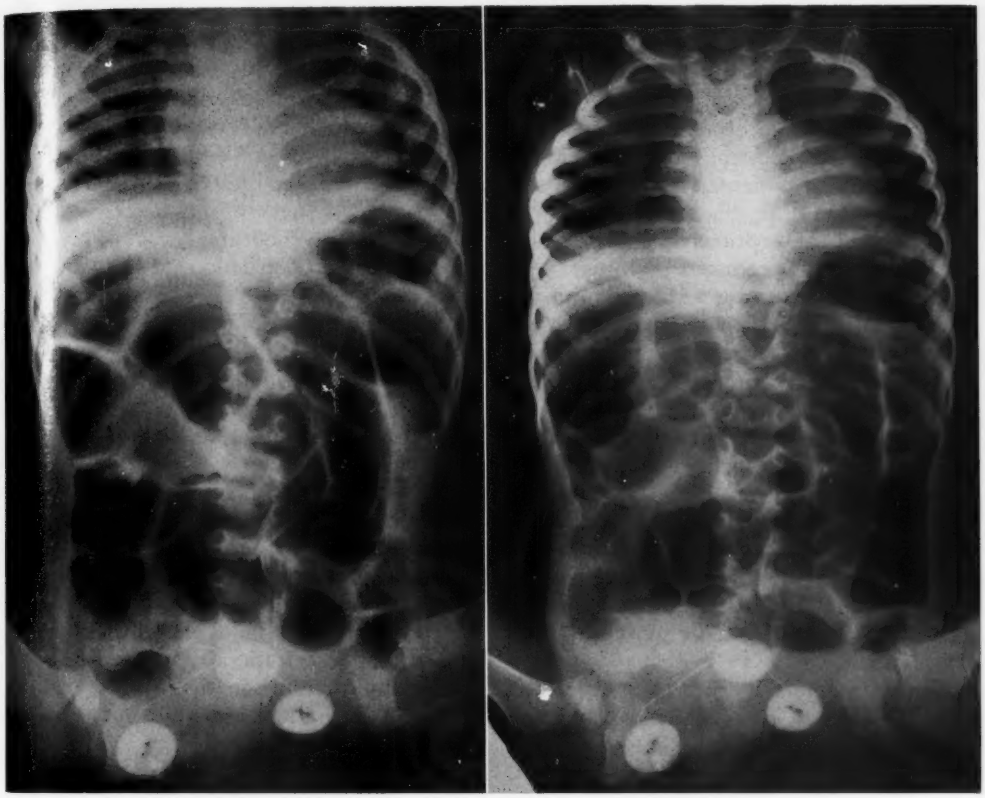

FIG. 2. Abdominal roentgenograms taken 23 days after a cystoplasty for exstrophy of the bladder, Case 5. Apparent adynamic ileus existed for 10 days postoperatively, followed by a week of improvement in intestinal function. Vomiting and abdominal distention then recurred, and these roentgenograms were obtained. They were interpreted as showing probable large intestinal obstruction. At laparotomy an ileocolic intussusception was noted.

tinal wall layers, three on each side, seen only in intussusception.

The intussuscepted intestine was regarded as viable in all instances. A simple manual reduction was carried out in 5 patients and an exteriorization resection in 1, that of Case 2.

The postoperative course after the second laparotomy was uneventful, although major problems associated with their primary disease remained in 2 patients, Cases 4 and 5. There have been no recurrences or other complications referable to intussusception during the periods of observation noted (Table I).

DISCUSSION

Numerous workers have described the occurrence of certain intra-abdominal complications, peculiar to the early postoperative period after abdominal surgical procedures in adults. Glenn described postoperative acute cholecystitis in 1947. Postoperative acute pancreatitis was reported by Sparkman. Perforation or hemorrhage from duodenal ulcer following unrelated abdominal procedures was studied by Penner and Bernheim, and later by Goldfarb and Saltzstein. Gannon and Harrington and Rose have described acute intestinal volvulus in the early postoperative state.

Among these conditions, only postoperative volvulus is found with any regularity among infants and small children. Intussusception, however, assumes a corresponding role in this age group. It occurs with three times the frequency of postoperative volvulus among patients seen in this pediatric center and represents almost 3 per cent of all intussusceptions observed.

The symptoms produced by intussusception in the postoperative state are quite distinct from the symptomatology of the more common variety of idiopathic, ileocolic intussusception. They are, on the other hand, similar to those previously reported by Kristiansen and Snyder in a series of exclusively enteric intussusceptions. Blood is usually not found in the stools, and an abdominal mass is rarely if ever palpable. Vomiting and abdominal distention are the only prominent clinical features of intussusception in this situation. The symptoms are thus those of acute small intestinal obstruction.

Etiologic factors in the majority of patients in whom early postoperative intestinal obstruction develops in any age group are: (a) adynamic ileus, (b) adhesions or bands, and (c) anastomotic malfunction, when there has been an anastomosis. The present series is obviously abstracted from this much larger clinical group, and in each case these diagnoses, i.e., of adynamic ileus and adhesions were entertained for the greater portion of the course prior to laparotomy.

It is probable that intestinal suction only adds to the diagnostic confusion in this unique group of cases, although, were it possible to advance the tube to the site of intussusception and outline it with contrast material, a definite preoperative diagnosis could be established. Barium enema would have made the diagnosis apparent in only 1 of these cases.

There are no roentgenologic or clinical criteria by which one can clearly differentiate between the cases of acute intussusception and the cases of mechanical ileus secondary to adhesions postoperatively. Certain factors, however, are helpful. Postoperative intussusception is known to occur in adults but is certainly more common in infancy and early childhood. The clinical pattern of initial improvement in intestinal function progressing over several days or more and followed by a very sudden reversal of this trend suggests intussusception. Abdominal roentgenograms revealing evidence of mechanical obstruction and ileus are usually seen and are often associated with moderate amounts of intra-abdominal fluid.

A granulocytic leukocytosis of major proportions is usually produced by intussusception. The development of such a symptom complex as herein outlined after abdominal procedures which do not commonly produce either significant ileus or adhesions is suggestive.

In 3 cases, ileoileal intussusception followed an ileal resection, a diverticulectomy. The anastomosis appeared at operation to be the "leading" point in only 1 of these cases. However, the deep inversion produced by a closure in three layers may be sufficient to initiate intussusception as may any polypoid mass.

In the remaining cases, the cause of postoperative intussusception must be assumed to be related to the disorganized peristaltic activity which accompanies the return of intestinal function after any laparotomy.

Effective treatment of postoperative intestinal obstruction by intraluminal suction is fraught with technical difficulties when applied to infants and small children. A rapid passage of the tube through the intestinal tract with relief of obstruction must be the only criterion of success when employing this method. Any result short of this makes further reliance upon this technique appear hazardous.

SUMMARY

Postoperative intussusception is a distinct complication, occurring with sufficient frequency in infants and small children to warrant special consideration when obstruction occurs after laparotomy. Such in-

tussusceptions are usually confined to the small intestine. They are rarely associated with rectal bleeding or a palpable abdominal mass. The development of vomiting and abdominal distention after an initial return of gastrointestinal function are the characteristic features. Roentgenograms usually suggest mechanical obstruction with intra-abdominal fluid, and a marked leukocytosis is common.

Therapy by intraluminal suction in cases of apparent adynamic ileus or adhesive obstruction in this age group should be brief and conducted with recognition of the existence of postoperative intussusception as a significant clinical entity.

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MORPHOLOGIC MODIFICATIONS IN GRANULOMATOUS THYROIDITIS DUE TO CORTISONE ADMINISTRATION

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In a recent clinicopathologic review of 36 cases of subacute granulomatous thyroiditis, the progressive alterations in the development of the pseudogranuloma have been carefully described (1). In the early stages of development, single acini in a patchy fashion were involved throughout the entire gland. These follicles were tremendously distended and the lining epithelium showed marked hypertrophy and hyperplasia. Since the innermost epithelial cells frequently failed in cytoplasmic division, there resulted multinucleated cells which, when applied to colloid, suggested phagocytic activity. Although the colloid became progressively more dense, the margins not infrequently presented a scalloped or serrated border. With hematoxylin and eosin and special stains, the basement membrane of the acini appeared intact. There were minimal perifollicular inflammatory cell infiltration and no abnormal vascular changes. Initiation of the midstage was heralded by disruption of the basement membrane which was followed by extreme neutrophilic infiltration of the colloid. In time, the neutrophils were replaced by numbers of lymphocytes and macrophages. Thereafter, the acinus collapsed and there was progressive loss of the remaining acinar cells. In the late stage, there was focal increase in collagen, and the area of scarring became more dense and less cellular. Nearby blood vessels showed obliterative endarteritis.

This anatomic progress of the disease indicated that unknown initiating factors antedated the disruption of the follicle. Therefore, the autoimmune mechanism was a complication and not the basic pathogenesis of the disease. Furthermore, in anatomically proved subacute granulomatous thyroiditis, there is inadequate correlation between the serum antibody titer and the extent and severity of the disease. Simple disruption cannot be the sole pathogenesis, for, with subtotal thyroidectomy for multiple causes, surgical disruption of many acini fails to produce any consistent significant rise in antibody titer.

In this series, 7 white female patients had been treated preoperatively with steroids (Table I.). Because of failure of clinical response or recurrence of symptoms, with sudden onset in 86 per cent and gradual in 14 per cent, indicating continued progress of the disease, these patients underwent subtotal thyroidectomy. The histories and the tissues of these patients were carefully compared with the findings in the other, untreated patients in order to determine the alterations which could be attributed to the cortisone therapy. Upper respiratory infection initiated complaints in 60 per cent of these patients.

RESULTS

The clinical complaints and the physical findings in a group of 36 patients have been previously described (1). On review, there were 7 patients refractory to cortisone who could not be distinguished from the general group by any feature in their history or physical or laboratory findings. The pertinent clinical features and physical findings are summarized in Tables I and II. The average total dose of cortisone was 443 milligrams, and the average daily dose was

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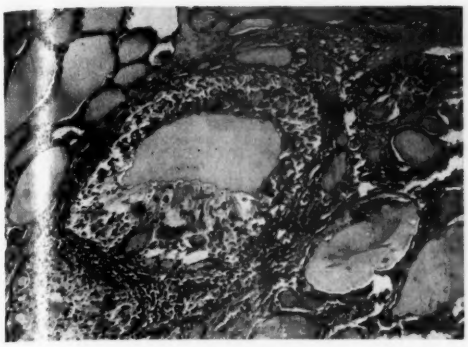

FIG. 1. Photomicrograph of untreated pseudotuberculous granuloma showing marked hypertrophy and hyperplasia of lining cells. Hematoxylin and eosin, ×43.

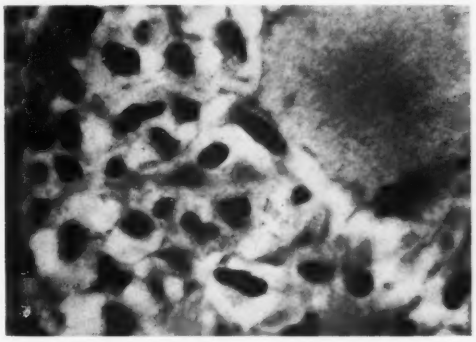

FIG. 2. High power photomicrograph showing detail of the untreated hypertrophied epithelial cells. Hematoxylin and eosin, ×392.

35 milligrams. The treatment period averaged 20 days.

In general, the glands resected from the steroid treated patients were smaller in size and less vascular than the glands of those who had not received therapy. However, the typical gross bilateral involvement was apparent. The tissues were tan, moderately firm and lobulated, and contained no areas of hemorrhage, cystic degeneration, or calcification.

The development of the pseudotuberculous granuloma in three distinct stages believed to represent the natural history of the disease was altered quantitatively.

In the early stage, the glands in these 7 patients differed quantitatively from those in the untreated group. In general, the numbers of acini involved seemed to be less in the treated group. The outstanding difference was that the lining epithelial cells showed considerably less hyperplasia and hypertrophy. In the untreated group, it was common to see a layer 5 cells in thickness representing the degree of acinar epithelial hyperplasia (Figs. 1 and 2). In the treated series, this layer was usually 2 or 3 cells in thickness. The distention, the character of the colloid, the presence of multinucleated cells, the absence of inflammatory cells, and vascular changes were similar although less marked (Figs. 3 and 4). The midstage in the development of the granuloma characterized by disruption of the basement membrane

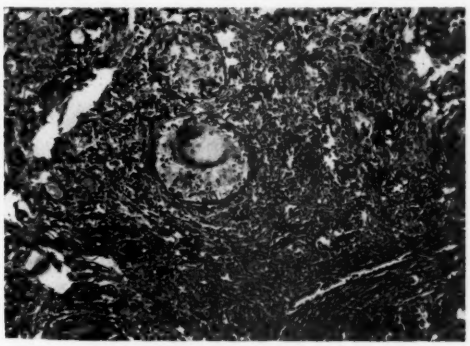

FIG. 3. Photomicrograph of granuloma in patient receiving cortisone shows quantitative reduction of all morphologic features of the pseudotuberculous granuloma. Hematoxylin and eosin, ×22.

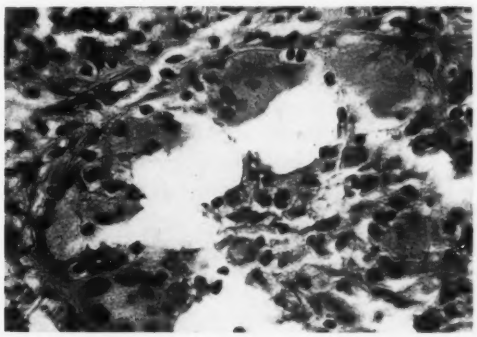

FIG. 4. Photomicrograph of cellular detail of the granuloma in patient given cortisone therapy showing depression of cellular hyperplasia. Hematoxylin and eosin, ×196.

TABLE I.—PRESENTING COMPLAINTS OF 7 PATIENTS TREATED PREOPERATIVELY WITH CORTISONE

Complaints	*Per cent of patients*
Neck pain	43
Enlarged thyroid	30
Swelling of the neck	14
Fever	14
Dysphagia	14

TABLE II.—SIGNS AND SYMPTOMS IN PATIENTS REFRACTORY TO CORTISONE

	Per cent of patients
Symptoms	
Weight loss	43
Dyspnea	43
Neck tenderness	30
Dysphagia	14
Fever	14
Anorexia	14
Signs	
Swelling of the neck	100
Tumor of the neck	71
Tenderness of the neck on palpation	71
Tremor of the hands	14

was also present. However, the number of neutrophils and extent of their infiltration was moderately reduced. In time, these neutrophils were replaced by a smaller number of lymphocytes and macrophages. In the late stage there was less of the acinus with collapse fibrosis. Again, the degree of scarring and collagen formation was less than that observed in the untreated group.

DISCUSSION

In this group of 7 patients refractory to steroid therapy, there seemed to be some direct quantitative influence of the steroids on the number and degree of the development of the pseudotuberculous granulomas. Therapy appeared to reduce the number of acini involved, the degree of acinar cell hypertrophy and hyperplasia, the degree of acute and chronic inflammatory cell infiltration subsequent to rupture of the acinus, and the amount of scarring subsequent to collapse fibrosis of the destroyed acinus. However, steroid therapy does not alter the basic pathogenesis of the pseudotuberculous granuloma. The clinical response of granulomatous thyroiditis to steroid therapy is probably dependent on the quantitative influence of steroids on the anatomic progress of the granulomas.

SUMMARY

In a clinicopathologic review of 36 cases of chronic granulomatous thyroiditis, there were 7 patients previously treated with steroids. These patients were clinically refractory to this medical regimen and subsequently underwent subtotal thyroidectomy. These cases were compared with those in which subtotal thyroidectomy was performed as primary therapy without the use of cortisone. In general, the steroid influenced the number and degree of the development of the pseudotuberculous granuloma but it did not basically alter the pathogenesis of the disease. It is believed that in patients treated successfully clinically with steroids there is effective suppression of the pseudotuberculous granuloma formation.

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AN EVALUATION OF GASEOUS OXYGEN PERFUSION AS A METHOD FOR MAINTAINING RENAL VIABILITY DURING PERIODS OF COMPLETE ISCHEMIA

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WITHIN THE PAST SEVERAL YEARS a number of investigators have demonstrated that tissues and organs may be maintained in a viable and functional state for a limited time by the perfusion of gaseous oxygen into the arterial system. In the studies reported upon thus far, an evaluation of the long term effect on the functional capacity of these tissues has not been attempted.

The sensitivity of the kidney to relatively limited periods of anoxia has been well documented by a number of observers. The present evaluation concerns the long term comparison of renal function in dogs after periods of complete renal ischemia and similar periods of occlusion of the renal artery with simultaneous gaseous oxygen perfusion.

METHODS AND RESULTS

Fourteen adult mongrel dogs were used in the study. The animals were lightly anesthetized with ether, and ventilation was maintained through an endotracheal tube attached to a respirator. A left flank incision was made and the capsule of the left kidney was freed from the perirenal tissue. The renal pedicle was identified and carefully dissected, leaving only the major vessels and ureter intact. The small ureteral artery was also identified and a 1 centimeter proximal segment ligated and excised. After this extensive dissection, the blood supply of the left kidney was dependent entirely upon the major renal vessels and the few collateral channels remaining within the wall of the left ureter. The animals were then divided into 3 groups as follows:

Group 1. Four animals in this group underwent complete occlusion of the renal artery and vein with rubber shod arterial clamps for a period of 2 hours (Table I). Care was taken to apply the arterial clamp prior to occluding the vein. In each instance the kidney immediately blanched and diminished in size. The removal of the clamps after a period of 2 hours resulted in evidence of reestablishment of renal circulation. The animals were subsequently followed up for periods of from 1 to 7 months. Intravenous pyelograms obtained at intervals during this time failed to demonstrate evidence of left renal function in any animal in this group. In dogs 2, 3, and 4, removal of the normal right kidney resulted in prompt death from uremia, as demonstrated by a rising serum urea nitrogen. The left kidney was found to be markedly atrophic in each instance (Fig. 2). Microscopic studies revealed marked tubular degeneration and scarring with partial preservation of the glomerular pat-

TABLE I.—COMPLETE ISCHEMIA OF THE LEFT KIDNEY FOR 2 HOURS IN CONTROL GROUP 1

Dog No.	*Period of follow-up, mos.*	*Evidence of left renal function*	*Final kidney weight, gm.*	
			Right	*Left*
1	1	None	37.0	16.0
2	7	None	37.5	8.0
3	4	None	44.5	6.0
4	4	None	41.0	5.0

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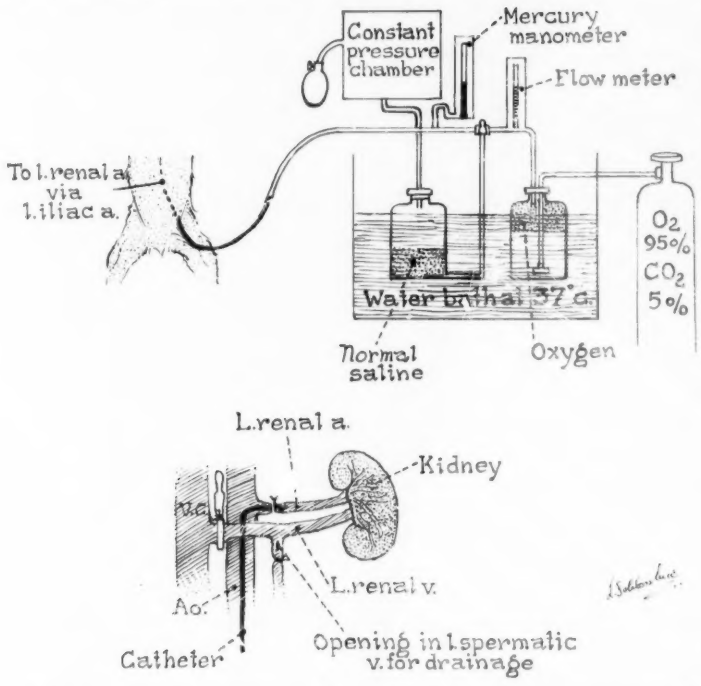

FIG. 1. Diagram of method for perfusing normal saline and oxygen into the left renal vascular system.

tern. There was no gross or microscopic evidence of thrombosis of the renal vascular system.

Group 2. In 3 animals in this group, the left kidney was isolated in the manner already described for group 1. A longitudinal incision was then made in the left inguinal region. A special metal cannula was introduced into the left iliac artery, passed into the aorta, and subsequently into the orifice of the left renal artery where its flanged tip was secured by a ligature. An arterial clamp was then applied to the distal portion of the left renal vein. The left ovarian or spermatic vein was ligated and incised proximally. The metal cannula was connected to the system as shown in Figure 1. Normal saline was then perfused into the cannula under systemic arterial pressure, subsequently flushing through the left renal artery, kidney, and vein, with final escape through the proximal cut end of the left ovarian or spermatic vein. Flushing of the left renal vascular system was continued until the escaping fluid was clear with no gross evidence of residual blood. The time required for the accomplishment of this procedure never exceeded 5 minutes, and the total quantity of saline used for this purpose was not greater than 250 cubic centimeters. The kidney was then permitted to remain in an unperfused state for a period of 2 hours. Following this, the left renal blood flow was restored by releasing the metal cannula from the orifice of the left renal artery, removing the clamp from the left renal vein, and ligating the proximal stump of the left ovarian or spermatic vein. In each instance there was evidence of immediate re-establishment of left renal circulation.

The 3 animals were followed subsequently for periods of from 7½ to 8½ months. In

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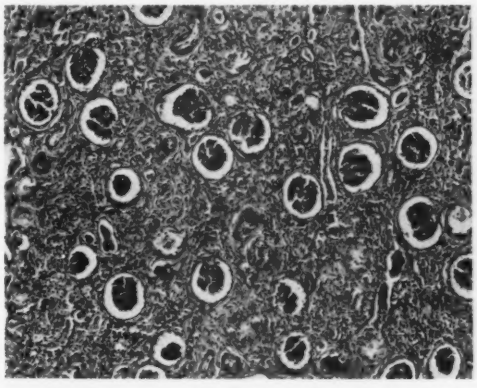

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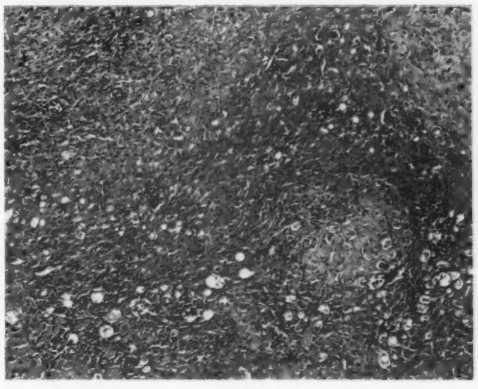

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FIG. 2. a, Gross specimen of normal right kidney and markedly atrophic left kidney after 2 hours of complete left renal ischemia. Photomicrographs of representative areas of the: b, cortex and c, medulla of the left kidney demonstrate marked tubular degeneration and scarring, animal 4.

only 1 animal was there evidence of left renal function as indicated by intravenous pyelograms. Removal of the normal right kidney in this animal resulted in a prompt elevation of the serum urea nitrogen to 135 milligrams per cent, at which level it remained stable. Subsequently, the left kidney was found to weigh 12.5 grams, compared to a right kidney weight of 58.3 grams. Microscopic examination of the left kidney revealed moderate to severe atrophy and scarring of the tubules. There was marked gross atrophy of the remaining 2 kidneys in this series with microscopic evidence of severe tubular degeneration and scarring. There was no gross or microscopic evidence of obstruction of the vascular system.

Group 3. The procedure followed in the 7 animals in this group paralleled the initial steps outlined for group 2 (Table III). The metal cannula which was introduced into the left renal artery by way of the left iliac artery and aorta was connected to the system as seen in Figure 1. Perfusion of normal saline, as noted in group 2, was followed by a warm, humidified mixture of gaseous oxygen, 95 per cent, and carbon dioxide, 5 per cent, under initial pressures of 120 to 150 millimeters of mercury. As this gaseous mixture filled the renal vascular system, the perfusion pressure gradually decreased to 80 to 100 millimeters of mercury with an average flow of 150 cubic centimeters per minute. At the end of varying periods, as will be specified, perfusion with normal saline was reinstituted. This saline flush was continued for several minutes until there was no gross evidence of gas remaining in the left kidney. Normal renal blood flow was then reconstituted as outlined in group 2.

In 4 animals in this group, gaseous perfusion was maintained for 2 hours. These dogs were followed up for periods of from 1 week to 1 year. In each, there was evidence of left renal function as demonstrated by intravenous pyelograms (Fig. 3). Animals 8 and 9 underwent right nephrectomy 7

FIG. 3. An intravenous pyelogram demonstrating left renal function 1 year after gaseous oxygen perfusion during a 2 hour period of renal artery occlusion, animal 8.

months later, and subsequent determinations of the serum urea nitrogen during the succeeding 5 months failed to demonstrate an elevated serum level. It is interesting that in 2 of the 4 animals, Nos. 8 and 10, the left kidney was supplied by 2 arteries arising separately from the aorta. At operation, 1 artery was sacrificed while the other was perfused. Final examination of the left kidney in animal 8 revealed complete atrophy and scarring of the posterior one-half of the kidney which was supplied by the sacrificed vessel. Microscopic study of the anterior one-half of this kidney revealed only evidence of minimal scarring and tubular atrophy. Gross and microscopic examination of the left kidney from animal 9 which was followed up for 1 year, similarly revealed only minimal tubular scarring and atrophy (Fig. 4). This relative lack of histologic alteration was in direct contrast to the changes noted in the kidneys removed from the animals in groups 1 and 2.

TABLE II.—NORMAL SALINE FLUSH OF LEFT RENAL ARTERY AND KIDNEY FOLLOWED BY 2 HOURS OF COMPLETE RENAL ISCHEMIA IN CONTROL GROUP 2

Dog No.	*Period of follow-up, mos.*	*Evidence of left renal function*	*Final kidney weight, gm.*	
			Right	*Left*
5	8½	Yes	58.3	12.5
6	7½	None	60.0	8.0
7	7½	None	50.0	4.0

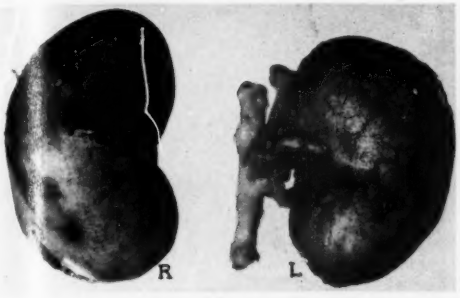
TABLE III.—GASEOUS OXYGEN PERFUSION OF LEFT RENAL ARTERY AND KIDNEY IN GROUP 3

Dog No.	*Duration of perfusion, hrs.*	*Length of follow-up*	*Evidence of left renal function*	*Final kidney weight, gm.*	
				Right	*Left*
8	2*	1 year	Yes	48.5	40.0
9	2	1 year	Yes	35.5	32.0
10	2*	2½ weeks	Yes	53.0	50.0
11	2	1 week	Yes	—	—
12	3*	2 weeks	Yes	45.5	29.8
13	4	1 week	Yes	41.0	31.0
14	4	6½ months	None	48.0	3.0

*Left kidney supplied by 2 renal arteries arising separately from the aorta.
One artery only perfused in each instance with occlusion of the other artery.

In 1 animal, gaseous perfusion of the left kidney was continued for a period of 3 hours. This kidney also was supplied by 2 separate renal arteries, 1 of which was occluded by a bulldog clamp while the other was perfused. During the subsequent 2 weeks there was evidence of left renal function as demonstrated by intravenous pyelography. Gross and microscopic examination of the left kidney at the end of this period showed thrombosis of that portion of the renal vascular system which originated from the artery that had been clamped during the period of perfusion. There was marked atrophy and necrosis of the kidney in the area supplied by this vessel. There was minimal alteration in the remainder of the kidney (Fig. 5).

In the remaining 2 dogs, the left renal artery was perfused with the gaseous mixture for a period of 4 hours. Renal function was demonstrated subsequently on the left side in 1 of these animals by intravenous pyelography, but there was marked gross alteration of this kidney noted after a period of 1 week. The other animal was followed up for 6½ months with no evidence of left



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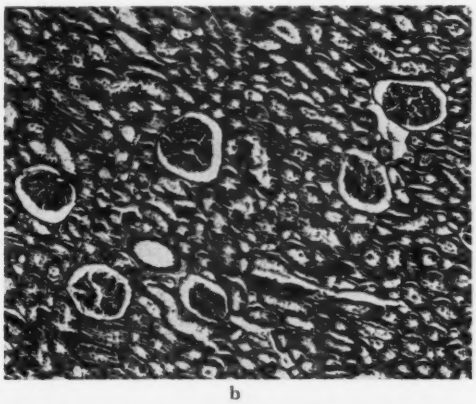

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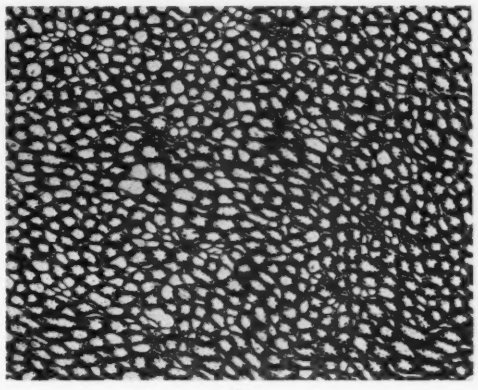

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FIG. 4. a, Gross speciman of normal right kidney and relatively unaltered left kidney after 2 hours of left renal artery occlusion and gaseous oxygen perfusion. Photomicrographs of representative areas of: b, cortex and c, medulla of the left kidney demonstrate minimal histologic alterations, animal 9.

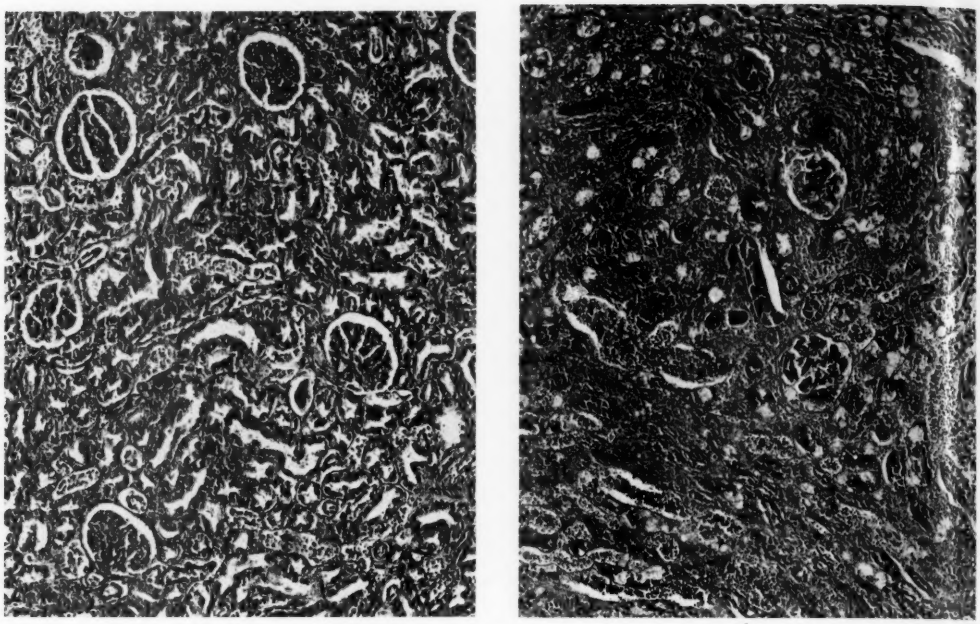
renal function demonstrated by intravenous pyelography. Right nephrectomy at the end of this time resulted in a prompt elevation of the serum urea nitrogen, greater than 200 milligrams per cent, and subsequent death from uremia. The left kidney was found to be markedly atrophic with prominent tubular atrophy and scarring. The vascular system appeared to be patent.

DISCUSSION

The sensitivity of the kidney to limited periods of ischemia has been documented by a number of investigators. It has been found by DeBakey that the human kidney may tolerate occlusion of the renal artery for periods of as long as 45 minutes, but extension beyond this time appears to be increasingly hazardous under normothermic conditions. Evidence has been advanced that the kidneys of various animals may be capable of tolerating longer periods of ischemia, but Creech has observed succinctly, "The functional damage induced by various occlusive arterial procedures is proportional to the amount of collateral blood flow to the kidney during the period of occlusion."

The results obtained in the control series, group 1 of the present investigation, indicate a slightly greater sensitivity of the dog to renal ischemia than has been demonstrated by Friedman, Murray, and Scheibe and their associates. The careful interruption of renal blood flow for 2 hours is thought to explain the uniform observations of subsequent marked renal atrophy and scarring.

Flushing of the renal vascular system with normal saline prior to complete vascular occlusion, as performed in group 2, may afford some degree of protection to the kidney from the effects of ischemia. Murray and Webb and their co-workers have utilized this procedure during periods of interruption of both renal and coronary artery blood flow. This technique may protect the organ by preventing thrombosis of the small peripheral vascular channels during such periods of complete ischemia. The results



a b

FIG. 5. Photomicrographs of kidney after gaseous oxygen perfusion of only 1 branch of the renal artery during 3 hours of complete renal ischemia, contrasting: a, viable perfused segment and, b, necrotic nonperfused area, animal 12.

obtained with this method in the present series are inconclusive, but do not appear to compare favorably with those achieved with gaseous perfusion.

Gaseous oxygen perfusion of the vascular system of the kidney during periods of occlusion of the renal artery, as defined in group 3, would appear to afford increased protection to the kidney during this time. The evidence for such protection is apparent by comparison of the results obtained after complete renal ischemia with those achieved after gaseous perfusion for a similar period of time. The functional and histologic observations in this latter group are in marked contrast to those obtained in the control series, with evidence of intact excretory function as demonstrated by intravenous pyelography together with minimal gross and microscopic alteration. The protective benefits of gaseous perfusion of the kidney would appear to extend to 3 and perhaps 4 hours, although the number of animals observed for these periods is insufficient to allow formulation of a definite conclusion.

Previous investigations have demonstrated that, in the presence of gaseous oxygen perfusion, certain tissues and organs maintain their viability and function (5, 7). The presence of high concentrations of oxygen in the gaseous perfusion would appear to be critical, since either substitution of nitrogen or cessation of oxygen perfusion has been demonstrated to result in immediate impairment of the functional activity of the organ.

Previous experiments utilizing the technique of gaseous oxygen perfusion have been acute studies without an evaluation of the long term effect of the procedure (5, 7). The results in the present series indicate that the protective benefits of gaseous oxygen perfusion during periods of prolonged ischemia are maintained subsequently with retained functional activity. This protection

may result partially from the complete removal of blood from the organ and the prevention of intravascular thrombosis during the period of arterial occlusion. However, it would appear to be primarily dependent upon the ability of the renal cells to utilize the oxygen perfused in the gaseous state.

SUMMARY

Previous investigations have demonstrated the sensitivity of the kidney to limited periods of ischemia. Similarly, acute studies have indicated that tissues and organs may be maintained in a viable and functional state for limited periods by the perfusion of gaseous oxygen into the arterial system. In the present experiments, a number of observations have demonstrated long term survival and function of the kidney perfused with gaseous oxygen during periods of complete interruption of renal blood flow.

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AN EXPERIMENTAL STUDY OF THE ROLE OF THE KIDNEY IN HYPERCHLOREMIC ACIDOSIS

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THE ROLE of the absorption of electrolytes by the colonic mucosa in the experimental production of hyperchloremic acidosis was discussed in a previous article (2). Diversion of urine to the colon was accomplished by anastomosing the trigone of the bladder to the rectum in one group of dogs, to the upper part of the colon in another group, and to the midportion of the colon in a third group. Further studies were then carried out to determine whether surgical destruction of renal tissue would precipitate the development of hyperchloremic acidosis or if such factors as disease of the kidney secondary to ureteral obstruction, excretion of waste products absorbed from the colon, and potassium deficiency had contributed to the development of this condition. Animals in which acidosis was induced by ammonium chloride were used to provide control data. The results of these investigations covering the possible role of the kidney in the development of hyperchloremic acidosis are reported herein.

METHODS

Reduction of renal tissue. In 11 animals, 3 with diversion of urine to the rectum and 8 with diversion to the upper or middle portion of the colon, the functioning renal tissue was reduced 60 to 70 per cent by excising one kidney and partially destroying the other with the aid of a cork-borer type of punch fitted with an obturator. Plugs of renal tissue were cored out through the entire thickness of the remaining kidney over about two-thirds of its length. The resulting defects were filled with gelfoam to prevent hemorrhage. As each piece of tissue was removed, a dark, wedge-shaped area of ischemia appeared in the medulla and cortex peripheral to the lesion and similar areas were produced when a second series of defects was made between those of the first series (Fig. 1). Considerable scarring of one pole of the kidney eventually developed after this procedure, while the other pole underwent compensatory hypertrophy and contained the only uninjured renal tissue (Fig. 2). The purpose of reducing the amount of functioning renal tissue was to determine: (1) whether acidosis would be precipitated or aggravated and the survival time of the animal shortened, and (2) whether any renal lesions, due to causes other than ureteral obstruction, would develop in the remaining segment of the kidney.

Excretory urograms. Excretory urograms were taken at intervals in 31 dogs to determine whether or not ureterectasis and pyelocaliectasis were present. In 3 instances, roentgenograms were taken immediately before operation and again after the onset of acidosis. Any dilatation of the urinary tract that was observed was graded 1 to 4.

Nephrostomy and tests of renal function. The functional status of the kidney or kidneys was assessed in 16 dogs to determine: (1) whether any acidosis present could be explained on the basis of renal insufficiency and (2) whether renal insufficiency had

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Abridgment of thesis submitted by Dr. Hayward to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Surgery.

occurred in the absence of pyonephrosis. For this purpose, bilateral nephrostomy was performed. In 10 of the 16 dogs—3 with reduction of renal tissue—urine had been diverted to the rectum; these animals were observed for 6.0 to 12.5 months, an average of 10.4 months. In 4 dogs—1 with reduced renal tissue—the urine had been diverted to the upper third of the colon; the follow-up period was 4.5 to 10.5 months, an average of 8.5 months. In 2 dogs, the bladder had been anastomosed to the middle third of the colon; the follow-up periods were 8.5 and 7 months. For the nephrostomy a length of No. 14 or 16 polyvinyl tubing, flanged at one end, was inserted into the ureter, passed along in a retrograde fashion with the aid of a curved introducer, and exteriorized through the substance of the kidney and abdominal wall. The ureter was ligated and divided below the flanged end of the tube; avulsion of the tube was prevented by fixing it to the renal capsule and parietal peritoneum with ivalon sponge (Fig. 3).

At nephrostomy, renal tissue was removed with the punch in 11 dogs so that the tissue could be studied histologically before operative trauma had produced any change. In addition, samples of urine were aspirated directly from one or both ureters at the time of nephrostomy for bacterial culture.

As soon as each animal had recovered from the ether anesthesia, the first urine excreted was collected and the *p*H, concentration of ammonia nitrogen, and specific gravity were determined. During the first few hours after operation, urine was collected to determine the rate of excretion of chloride. Urine was collected for a 3 hour period only and the values obtained were corrected to represent a 12 hour period, because excretion of chloride could be expected to decline rapidly after the first few hours. The rate of excretion of chloride for a particular interval was used as a quantitative estimation of the severity of hyperchloremia or as an indication of the magnitude of reabsorption of chloride from the colon with re-excretion in the urine.

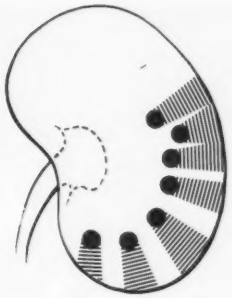


FIG. 1. Diagrammatic representation of the method used for reducing the total functioning tissue of a kidney.

During the first night after the nephrostomy and again on the fourth postoperative day, 12 hour specimens of urine were collected, together with samples of blood. The following data were then derived: (1) clearance of endogenous creatinine; (2) total chloride and potassium filtered by the kidney during a 12 hour period; (3) total chloride and potassium excreted in the urine and reabsorbed by the renal tubules during a 12 hour period; and (4) total chloride excreted and reabsorbed per 100 milliliters of glomerular filtrate.

Between the fifth and sixth postoperative days the dogs were deprived of water for 24 hours and a specimen of urine was collected for determination of specific gravity and the urine-to-blood concentration of urea. A sample of urine was also obtained for staining by Gram's method and for microscopic examination and test for albumin.

The determinations described in this section were expected to provide the following information: (1) the ability of the kidneys to produce acid urine and ammonia; (2) the rate of excretion of chloride immediately after nephrostomy; (3) the clearance of endogenous creatinine during the immediate postoperative period and again after 4 days; and (4) the relative amounts of chloride and potassium excreted in the urine and reabsorbed by the renal tubules during the immediate postoperative period and again after 4 days. In this manner the presence of a renal tubular defect contrib-

FIG. 2. The scarred, contracted pole and remaining hypertrophied pole of a kidney partially destroyed by the method described.

uting to the state of hyperchloremic acidosis or to the excessive urinary excretion of potassium might be demonstrated. Additional information desired concerned: (5) the ability of the kidneys to restore the levels of chloride and urea in the blood to normal; (6) the incidence of bacterial contamination of the urine as a result of diversion of urine to the colon; (7) the ability of the renal tubules to conserve potassium and concentrate urine and urea; and (8) the presence of renal damage as evidenced by the appearance of albumin, casts, or erythrocytes in the urine.

TABLE I.—RESULTS OF TESTS BEFORE AND AFTER REDUCTION OF TOTAL RENAL MASS IN 2 DOGS WITH DIVERSION OF URINE TO UPPER PORTION OF COLON

	Results with regard to reduction of the renal mass			
	First dog		*Second dog*	
Test	*Before reduction*	*After reduction*	*Before reduction*	*After reduction*
Blood urea, mgm./100 ml.	66.4	77.8	98.4	114.4
Serum chloride, mEq./l.	120.6	122.2	118.8	125.7
Plasma CO_2—combining power, mMl/l	16.68	13.22	16.45	15.38
Blood *pH*	7.171	7.068	7.122	7.079

Control group and studies of acidosis. Three normal dogs and 1 dog with about 70 per cent of renal tissue destroyed but without diversion of urine were subjected to the renal function tests described and then given ammonium chloride in 4 oral doses daily for a period of several months. The dose was varied to maintain the *pH* of blood and the concentration of serum chloride at approximately the same levels as those found in dogs in which severe hyperchloremic acidosis developed after diversion of urine to the cecum. Twice during the ensuing state of acidosis and again after the administration of ammonium chloride was stopped, renal function tests were repeated to determine whether there had been any detectable change in the functional status of the kidneys as the result of severe acidosis. From time to time, body weight was checked and the concentration of serum potassium determined. These data provided values for comparison with those obtained in dogs subjected to diversion of urine and nephrostomy.

Pathologic studies. Finally, whenever possible the kidneys from all dogs with diversion of urine, whether they died spontaneously or were killed because of poor health or after completion of renal function studies, as well as the kidneys from those animals given ammonium chloride were weighed and examined grossly and histologically. Sections were prepared from these specimens as well as from tissue obtained for biopsy at the time of nephrostomy. The sections were stained with hematoxylin and eosin, Mallory and Heidenhain, or Sudan IV stain.

RESULTS

Reduction of renal tissue. Reduction of total renal mass by the method described had no noticeable effect on the urea concentration of blood and hyperchloremia produced by diversion of urine to the rectum. However, a slight aggravation of hyperchloremic acidosis did result in cases in which the bladder had been anastomosed to the upper part of the colon (Table I). These changes became

less noticeable when hypertrophy of the remaining renal tissue occurred. No deterioration of health or shortening of survival time resulted.

Excretory urograms. Roentgenologic signs of obstruction were absent or minimal in the majority of the animals, and no obvious morphologic difference in the urinary tract was noted between the animals with acidosis and those with normal acid-base balance. In 2 dogs considerable dilatation, grade 2, of the ureters and renal pelves did develop, but excessive hyperchloremia or acidosis did not result. In 3 dogs in which the bladder had been anastomosed to the upper part of the colon, excretory urograms were made prior to operation and again 10 to 14 days later after acidosis had developed. No concomitant change was seen in the roentgenogram to explain the change in acid-base balance (Fig. 4a and b). Although anastomosis of the bladder to the rectum made it possible for the urine to diffuse throughout the colon, the absence of hyperchloremic acidosis suggested that the urine was retained in the rectum by fecal material most of the time. In 2 dogs in which the fecal stream had been diverted by means of proximal colostomy, the colonic pouch thus created regularly filled with the urographic dye, indicating that this portion of the colon behaved as an artificial bladder and, no doubt, offered an absorptive surface which was proportional to the size of the pouch. This finding probably explains the intermittent acidosis noted in these particular animals.

Tests of renal function. In all 16 instances, the first urine excreted after nephrostomy was acid in reaction, and the concentrations of ammonia appeared adequate. The specific gravity was low, especially in animals with both reduction of renal tissue and diversion of urine to the upper part of the colon. The rate of excretion of chloride was well above normal except when urine had been diverted to the upper part of the colon and the renal tissue reduced; however, there was only 1 animal in this category, and this result may have been fortuitous (Table II).

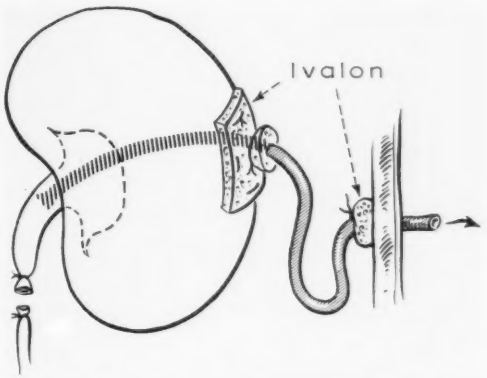


FIG. 3. Diagrammatic representation of the technique of nephrostomy.

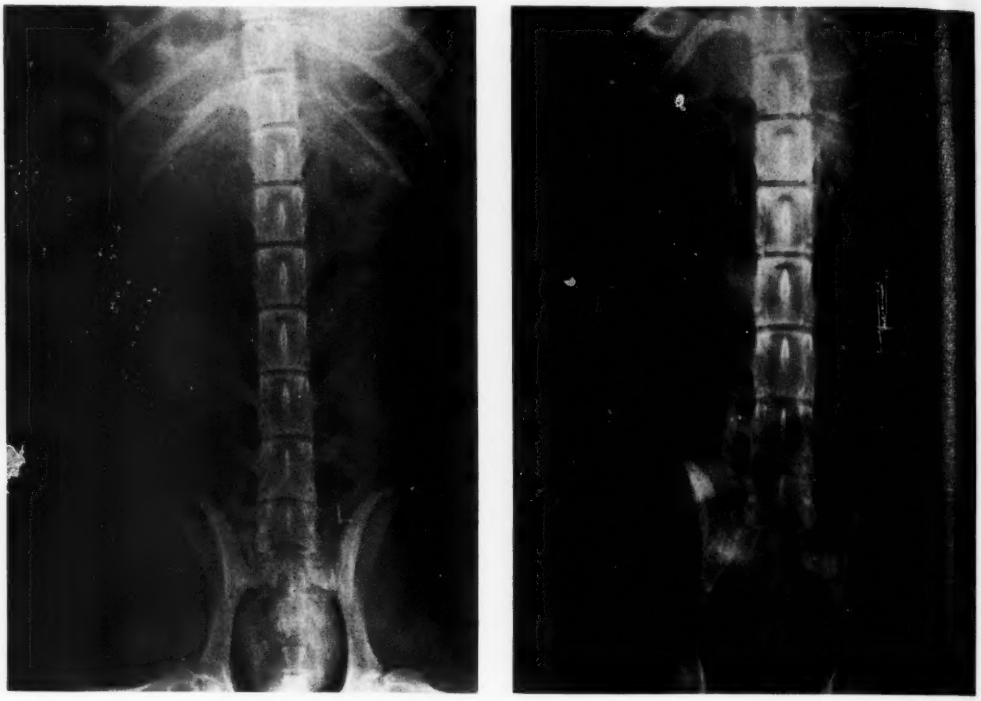
The clearances of endogenous creatinine for the first night after nephrostomy were similar to those found in normal dogs of similar weight and in animals with ammonium chloride acidosis; no significant change was seen by the fourth postoperative day (Table III).

Employing the results of the creatinine clearance tests, the 12 hour renal tubular reabsorption of chloride and the percentage of filtered potassium excreted in the urine were determined. All animals in the immediate postoperative period and those with ammonium chloride acidosis reabsorbed more chloride per 100 milliliters of glomerular filtrate than normal; however, these values were comparable in the two groups and returned to normal, or near normal, after recovery from the acidosis (Table III).

TABLE II.—AVERAGE URINARY *p*H, AMMONIA NITROGEN, SPECIFIC GRAVITY, AND CHLORIDE AFTER NEPHROSTOMY

	Dogs with diversion of urine to:		
Test	*Rectum*	*Upper colon*	*Middle colon*
*p*H	5.9	5.3	6.2
	5.8 (R)	5.4 (R)	
Ammonia nitrogen, mgm./100 ml.	63.9	96.2	34.3
	43.5 (R)	66.3 (R)	
Specific gravity	1.021	1.017	1.012
	1.015(R)	1.008(R)	
Chloride excretion,* mEq./12 hours	32.1	36.2	55.2
	21.1 (R)	10.9 (R)	

*Average normal urinary excretion of chloride in 4 control dogs during fasting was 4.8 mEq./12 hours.
(R), Dogs with reduced renal tissue.



a b

FIG. 4. The renal tract. a, Before diversion of urine. b, After appearance of severe acidosis following diversion of urine to upper part of the colon.

In all animals with diversion of urine to the upper or middle portion of the colon, the concentrations of blood urea and serum chloride returned to normal within 4 days after nephrostomy (Table IV).

All animals with either diversion of urine or ammonium chloride acidosis were able to concentrate urine and urea satisfactorily after being deprived of water for 24 hours although this ability was naturally limited in the case of animals with reduced renal tissue (Table V).

Examination of the urine. Culture of the urine aspirated directly from the ureters at the time of nephrostomy produced colonies of Escherichia coli, Aerobacter aerogenes, Streptococcus faecalis or Proteus in all except 1 animal. Usually more than one organism was found. In 6 of 7 control animals, urine aspirated from the bladder was sterile. Examination of urine collected via the nephrostomy tubes or from dogs with ammonium chloride acidosis failed to reveal any qualitative evidence of deterioration of renal function, such as albuminuria, hematuria, and the presence of casts.

The kidneys at necropsy. The average weights of the kidneys of 32 dogs in the various categories are shown in Table VI. In many instances, the remnant of kidney in animals with reduced renal tissue and diversion of urine underwent pronounced compensatory hypertrophy and weighed almost as much as both kidneys of comparable dogs.

Except for the hypertrophy in some of the cases, the kidneys were normal on gross examination in most instances, but in some animals the ureter and renal pelvis were moderately dilated; however, these struc-

tures and the kidneys themselves rarely showed signs of inflammation. Pyelonephritis was an unusual finding on histologic examination, but a number of the kidneys showed dilatation of the glomerular capillaries or of the convoluted and collecting tubules. The most significant finding, however, proved to be vacuolation of cells in the renal tubules. This change was observed more often when the bladder had been anastomosed to the upper part of the colon and almost invariably if the amount of functioning renal tissue had been reduced (Fig. 5). The kidneys from the dogs which were given ammonium chloride showed little hypertrophy and were normal upon histologic examination.

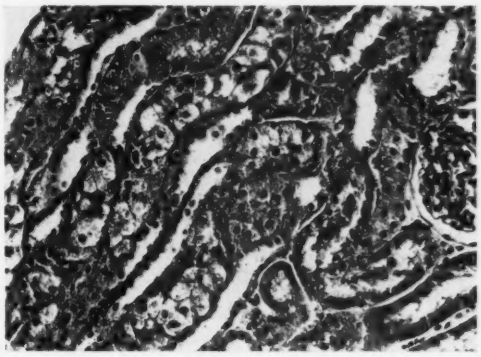


FIG. 5. Vacuolation of renal tubular cells.

COMMENT

Substantial reduction of renal tissue by surgical means did not play a significant role in the development of hyperchloremic acidosis following diversion of urine to the colon. Only in animals with diversion of urine to the upper portion of the colon was there some further increase of concentrations of blood urea and serum chloride and decrease in *p*H of the blood. Apparently destruction of renal tissue must be considerable before renal insufficiency rather than absorption of urinary products from the colon becomes responsible for the appearance of hyperchloremic acidosis.

Most excretory urograms, including several sets in which a urogram had been taken both before operation and again after acidosis had developed, were either within normal limits or demonstrated only minor obstructive changes. In no instance could these changes be correlated with the development of hyperchloremic acidosis.

Examination of urine collected immediately after nephrostomy showed that most dogs were passing urine of rather low specific gravity—diuresis—and invariably low acidity; the concentration of ammonia was probably adequate in all cases. Although the differences in concentration of ammonia between those animals with diversion of urine to the rectum and those with diversion of urine to the upper or middle portion of the colon were not pronounced, the diluteness of the urine obtained from the latter animals may have accounted for this finding. The calculated rates of excretion of chloride per 12 hours in the early postnephrostomy period indicated that adequate amounts of chloride were being excreted, the values being far higher than those obtained in fasting control animals.

The creatinine clearances determined in these dogs were within the normal range, and no significant change occurred during a period of several days after nephrostomy.

In all cases the amount of chloride reabsorbed by the renal tubules per 100 milliliters of glomerular filtrate was of the same order as that seen in the control dogs with induced ammonium chloride acidosis. In every instance, the value returned to normal or near normal a few days after nephrostomy. It is unlikely, therefore, that any tubular defect was responsible for the observed hyperchloremia.

Although it is not strictly correct to speak of the amount of filtered potassium excreted and reabsorbed when secretion alone accounts for the presence of potassium in the urine, this seemed a convenient way of using these values as a test of renal function. Dogs with diversion of urine to the rectum were definitely excreting more potassium in the urine than those with diversion of urine to

TABLE III.—RESULTS OF TESTS AFTER NEPHROSTOMY IN DOGS WITH DIVERSION OF URINE AND IN THOSE WITH AMMONIUM CHLORIDE ACIDOSIS

		Dogs with diversion of urine to:			*Ammonium chloride acidosis*
Test	*Time*	*Rectum*	*Upper colon*	*Middle colon*	
Clearance of endogenous creatinine, ml. of blood per minute	(a)	26.7	25.4	41.5	29.2
		23.4 (R)	22.1 (R)		23.0 (R)
	(b)	33.2	25.6	41.6	29.2
		21.6 (R)	15.1 (R)		19.3 (R)
Tubular reabsorption of chloride, mEq./100 ml. of glomerular filtrate*	(a)	11.6	11.4	11.1	11.9
		11.5 (R)	12.4 (R)		11.4 (R)
	(b)	10.9	10.7	10.2	10.6
		10.9 (R)	11.0 (R)		10.8 (R)
Percentage of filtered potassium excreted†	(a)	25	23	11	40
		40 (R)	5 (R)		53 (R)
	(b)	4	2	3	27
		7 (R)	10 (R)		36 (R)

*Average normal chloride reabsorption was 10.8 mEq./100 ml. of glomerular filtrate.
†Average normal percentage of filtered potassium excreted in the urine was 19.
(R), Dogs with reduced renal tissue.
(a) On day of nephrostomy or during ammonium chloride acidosis.
(b) 4 days after nephrostomy or after cessation of administration of ammonium chloride.

the upper and middle portions of the colon in spite of the fact that the latter two groups, in which the largest amount of colonic surface was available for absorption of urinary products, represented the acidotic animals. This demonstrates not only that the dogs with acidosis were somewhat deficient in potassium but also that their kidneys were still capable of conserving this ion. Substantial reduction in the excretion of potassium occurred in nearly every dog several days after nephrostomy, indicating that the tubules were able to reabsorb and conserve potassium efficiently.

Further evidence of satisfactory renal function was provided by the observation that abnormal levels of the constituents of the blood returned to normal or near normal after nephrostomy. The animals were able to produce urine of satisfactory specific gravity and although the urine-to-blood ratios of the levels of urea were not as high as in some of the control animals, it must be remembered that the food intake was often poor during the first few days after nephrostomy. Results of urinalysis and examination of tissue obtained for biopsy gave an additional indication that no significant renal disease was present. Thus, although most animals showed some over-all quantitative reduction of renal function, no specific renal tubular defect could be found and, accordingly, the appearance of acidosis or potassium depletion in this study was not attributable to renal insufficiency. Significant renal damage, in turn, did not result from diversion of urine to the colon. Similarly, the tests employed showed that ammonium chloride-induced acidosis alone did not produce any recognizable renal disease.

Culture of urine collected at the time of nephrostomy almost always produced growth of one or more organisms, although gross infection of the urine was not apparent. Thus, bacterial contamination of the urine can generally be expected to occur when the urinary tract communicates with the colon.

At necropsy, only minor obstructive changes were occasionally observed in the urinary tract. In no instance was the renal parenchyma significantly reduced. Renal hypertrophy was usually seen in those animals which had been in reasonable health. In those dogs in which the renal tissue had been reduced surgically, the remaining portion of kidney often weighed as much as both hypertrophied kidneys from other animals; this probably explained the ability of these animals to maintain electrolytic balance.

By far the most interesting histologic change was vacuolation of tubular cells. Vacuoles were seen in the proximal, distal, and collecting tubules, but were most common in the distal and collecting segments. The vacuoles were clear, and the contents, if any, did not stain for fat. A number of them were small, and these gave the cells a somewhat foamy appearance, but the majority were large, causing a swelling that nearly obliterated the tubular lumen. Sometimes the cells were fragmented, with only a nucleus remaining and strands of cytoplasm projecting into the lumen; presumably in these cases the vacuoles had

been present but had ruptured. The presence of vacuoles could not be attributed to potassium deficiency or to pyelonephritis. Their histologic appearance resembled the cellular changes described by Hartman and Kulka and associates in conditions other than pure potassium depletion. The fact that they were observed more frequently in animals killed during the course of the experiment suggests that death from malnutrition or other causes was not the etiologic factor. In addition, the serum proteins of 2 malnourished dogs were found to be normal, yet in both dogs the characteristic vacuolar changes were found in the kidneys. A definite correlation was noted, however, with the excretory load presented to the kidneys. Two of 12 dogs with diversion of urine to the rectum had distinctive lesions and 1 of these had reduced renal tissue. Ten of 25 dogs with diversion of urine to the cecum or middle portion of the colon revealed vacuolar changes; of the 5 dogs in this group in which renal tissue had been reduced, only 1 dog failed to demonstrate vacuolation and this animal died from peritoneal abscesses and malnutrition. Acidosis per se was not responsible for the vacuolation, since the kidneys from the dogs treated with ammonium chloride were essentially normal. One may conclude, then, that the described changes were caused by the continued excretion of urinary products absorbed from the colon and that they occurred more frequently in animals having only a small amount of renal tissue to handle the excretory load. This does not mean necessarily that vacuolation was completely absent from the kidneys of most dogs in which the urine had been diverted to the rectum. Minimal changes were probably present in many of these cases, but is was necessary, for the purpose of classifying the results, to include only those kidneys demonstrating pronounced changes. The vacuolar lesions did not appear to cause reduction of renal function. Whether or not the lesions are reversible it has not thus far been possible to ascertain.

TABLE IV.—BLOOD UREA AND SERUM CHLORIDE AFTER NEPHROSTOMY IN DOGS WITH DIVERSION OF URINE TO UPPER AND MIDDLE PORTIONS OF COLON

Test	*Normal values*	*Before nephrostomy*	*After nephrostomy*
Blood urea, mgm./100 ml.	14.2–36.9	57.7	30.2
		87.7 (R)	60.0 (R)
Serum chloride, mEq./l...	107.1–113.6	118.9	106.7
		123.7 (R)	110.2 (R

(R), Dogs with reduced renal tissue.

TABLE V.—SPECIFIC GRAVITY AND UREA 5 DAYS AFTER NEPHROSTOMY OR AFTER ADMINISTRATION OF AMMONIUM CHLORIDE CEASED

	Control animals		*Dogs with diversion of urine to:*			
Test	*Av. value*	*No.*	*Rectum*	*Upper colon*	*Middle colon*	*Ammonium chloride acidosis*
Specific gravity	1.051	7	1.036	1.037	1.036	1.037
	1.033(R)	2	1.030(R)	1.020(R)		1.025 (R)
Urine-to-blood ratio of urea	200	7	90	138	145	113
	77 (R)	2	69 (R)	13 (R)		82 (R)

(R), Dogs with reduced renal tissue.

TABLE VI.—AVERAGE WEIGHTS OF KIDNEYS OF DOGS WITH DIVERSION OF URINE OR AMMONIUM CHLORIDE ACIDOSIS

		Weight, gm.	
Procedure	*Dogs*	*Right kidney*	*Left kidney*
Diversion of urine to:			
Rectum	7	36.5	38.0
	2(R)	69.5 (R)	
Upper or middle portion of colon	14	46.1	46.0
	5(R)		61.9 (R)
Ammonium chloride acidosis	3	36.2	39.7
	1(R)		44.4(R)

(R), Dogs with reduced renal tissue.

SUMMARY

1. Reduction of functioning renal tissue to the extent employed in this study did not aggravate experimentally induced acidosis, and so it is concluded that reduction of tissue must be great before the renal factor in hyperchloremic acidosis becomes important.

2. Excretory urograms showed that obstructive phenomena in the renal tract were rare with the types of diversion of urine to the colon employed, and that they certainly did not account for the development of hyperchloremic acidosis in the animals used in this study.

3. Even after prolonged diversion of urine to the rectum or upper part of the colon, no significant functional renal tubular defect

could be demonstrated. The kidneys returned the values of the electrolytes of the blood to normal and showed no significant decrease in their ability to produce ammonia, acidify urine, excrete chloride and creatinine, conserve potassium, concentrate urea, and produce urine of satisfactory specific gravity.

4. Urinalysis did not reveal any significant qualitative deterioration of renal function.

5. Bacterial contamination of the urine was almost always noted in animals in which urine was diverted. It can be expected to occur whenever there is anastomosis of the urinary tract to the bowel, even when the normal ureteral orifices are preserved.

6. Pyelonephritis was not a significant histologic finding. Dilatation of glomerular vessels was observed, but vacuolation of tubular cells was the most distinctive abnormality. Vacuolation was more severe when large areas of colonic mucosa had been exposed to urine and was more frequently seen when the amount of functioning renal tissue had been reduced.

7. Acidosis alone, induced by ammonium chloride, did not produce appreciable deterioration of renal function.

CONCLUSIONS

Following diversion of urine to the colon the development of hyperchloremic acidosis may be expected if a sufficiently large area of mucosa is exposed to urine. Unless renal function is greatly impaired, the kidney itself does not contribute to the imbalance of electrolytes. Although the excretion of urinary products absorbed from the colon does not appear to cause significant deterioration of renal function, histologic changes may result, and these vary in severity in proportion to the excretory load presented to the kidney.

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VILLOUS TUMORS OF THE RECTUM AND COLON CHARACTERIZED BY SEVERE FLUID AND ELECTROLYTE LOSS

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VILLOUS TUMORS of the large intestine are recognized as a distinct clinical and pathologic entity. The characteristic features of this lesion have been described in numerous excellent reviews, including those of Sunderland and Binkley, Ewing, and Wheat and Ackerman. The villous tumor usually occurs in the rectum or sigmoid colon of elderly individuals as a large sessile polyp with a broad, flat attachment to the bowel wall. Microscopically, the lesion is composed of delicate villous efflorescences covered by tall, columnar mucus-secreting epithelial cells. Large tumors with vast secreting surfaces may produce great quantities of mucus and cause a troublesome "pseudodiarrhea." A mucous or watery rectal discharge has been identified as a prominent symptom of villous tumors for many years. Reports in the recent literature describe a syndrome of severe fluid and electrolyte depletion associated with large villous tumors having profuse rectal discharge.

In 1954, McKittrick and Wheelock described the case of an 82 year old woman who experienced fainting, oliguria, and weakness due to electrolyte loss from a large villous papilloma of the rectum. This tumor secreted daily from 375 to 2,200 milliliters of clear, thin, slightly mucoid fluid containing up to 11 grams of sodium chloride. The blood nonprotein nitrogen reached 135 milligrams per 100 milliliters; the serum chloride fell to 70 milliequivalents, and the potassium to 1.32 milliequivalents per liter. Following repletion of fluid and electrolytes and resection of the rectal tumor, serum electrolytes returned to normal and all symptoms subsided.

Similar cases have since been described by: Fitzgerald; Starr, Mueller, and McKittrick; Cooling and Marrack; Gutierrez Blanco; Goldgraber and Kirsner; Jordan and Erickson; Roy and Ellis; Walters, Monks, and Chitty; Hoffman; Frye; and Mayfield and Milnor. These reports serve to establish that a syndrome of dehydration, hyponatremia, hypokalemia, hypochloremia, circulatory collapse, prerenal azotemia and metabolic acidosis can develop as a result of copious secretion of watery mucus from a villous tumor of the distal colon. This report is to add 2 case studies to the literature and to review a total of 18 cases of this syndrome.

CASE REPORTS

CASE 1. A 67 year old housewife was admitted to the Medical Service of the University of Alberta Hospital on 1 January 1956, for investigation of refractory diarrhea of 12 years' duration. Prior to 1944 she had had well formed stools 3 times a day "all her life." Initially, the episodes of diarrhea occurred about once a week and were characterized by the passage of up to 20 movements per 24 hours. Usually the stools were of small amount, dark brown in color, and semifluid. In addition, she frequently passed clear, watery fluid and flatus per rectum, particularly on awakening in the morning. She noted that raw vegetables and citrus fruits tended to precipitate and aggravate the watery discharge. When she restricted her diet to potatoes and rice the diarrhea tended to improve. She always had a good appetite and had increased in weight from 156 to 175 pounds over the 9 months prior to admission. There was no history of dyspepsia, fat intolerance, abdominal cramps, or melena.

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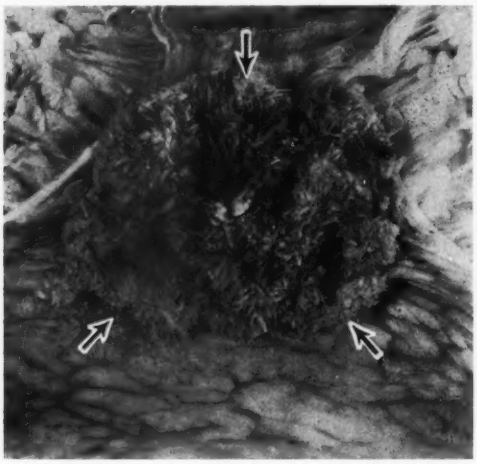

FIG. 1. Case 1. Villous papilloma encircling upper rectum (arrows) composed of innumerable filiform projections. Autopsy specimen, photographed under water.

During the summer of 1952, the patient felt weak, tired, and nauseated for a period lasting several weeks. Concurrently she experienced severe cramps in the calves of her leg. In the autumn of 1953 she was admitted to a hospital elsewhere in a state of circulatory collapse with a blood pressure of 70 systolic, 40 diastolic. Rapid clinical improvement followed the administration of intravenous saline solution. Similar attacks recurred during the summer of 1954 and in March and June 1955. Through correspondence with physicians who had treated the patient previously, it was learned that each episode had been characterized by gradually increasing malaise, ease of fatigue, nausea and vomiting, accompanied by hypotension, hyponatremia, hypochloremia, and reversible azotemia. Symptoms were always alleviated within a few days to a week, by the intravenous administration of physiologic saline solution. The concomitant diarrhea was attributed to an "irritable colon." Barium enema and gastrointestinal series were reported as "normal."

A prophylactic regimen of sodium chloride by mouth, 8 grams a day, was instituted in July 1955. With increased ease of fatigue and weakness, the patient would raise her daily intake of salt to 12 to 20 grams. She had also been advised to drink 16 to 18 glasses of water per day and voided a corresponding amount of urine. With episodes of "low salt state" she noticed a decrease in urine volume. There was no history of nephritis or renal calculi. The family history was noncontributory.

Physical examination revealed a pleasant, intelligent, obese, elderly, white woman who did not appear to be in ill health. General examination was within normal limits. The blood pressure was 130 systolic, 80 diastolic; pulse 80 per minute. No tumor was felt on rectal examination.

The urine was clear, straw colored, of acid reaction, and had a specific gravity of 1.012. Tests for glucose and albumin were negative; the sediment contained 5 to 10 white blood cells per high power field. Examination of the blood revealed a hemoglobin of 13.0 grams per 100 milliliters and a white cell count of 9,750, with 66 per cent neutrophils, 27 per cent lymphocytes, 4 per cent monocytes, and 3 per cent eosinophils; hematocrit 37 per cent; erythrocyte sedimentation rate 35 millimeters per hour. Eosinophil counts ranged from 192 to 212 cells per cubic millimeter. Serum albumin was 3.4 grams and globulin 2.6 grams per 100 milliliters. Urinary creatinine determination was 0.93 gram per 24 hours, 17-hydroxycorticosteroids

TABLE I.—BALANCE DATA AND SERUM ELECTROLYTES IN CASE 1

	Oral intake		*Urine*				*Rectal discharge*				*Serum*				*Blood urea*
Date	*of NaCl, mEq./- 24 hrs.*	*Body weight, kgm.*	*Volume ml./24 hrs.*	*Na*	*K*	*Cl*	*Volume ml./24 hrs.*	*Na*	*K*	*Cl*	*Na*	*K*	*Cl*	CO_2	*nitrogen, mgm./100 ml.*
				mEq./24 hrs.				*mEq./24 hrs.*			*mEq./liter*				
1- 1-56	430	76.0	120	1.3	2.3	2.0	2280	344	42.0	292	148	2.9	97	24	55
1- 8-56	270	74.6	1140	49.6	18.7	53.3	2685	—	—	—	143	4.6	105	23	25
1-19-56	220	79.5	2460	81.3	12.6	96.7	—	—	—	—	150	3.8	113	25	—
1-20-56	220	80.5	2000	53.8	16.9	58.2	2000	278	43.3	253	148	3.6	108	25	13
1-21-56	220	80.0	2500	48.7	6.7	87.0	2000	208	14.1	198	152	3.5	105	24	13
1-22-56	220	79.6	1800	23.9	15.1	31.4	1800	269	42.2	227	—	—	—	—	—
1-23-56	220	79.0	1990	13.9	11.8	17.0	2280	386	49.2	302	143	3.4	107	25	14
1-24-56	220	79.0	1930	10.0	17.4	8.2	2235	306	50.5	286	—	—	103	27	16
1-25-56	220	79.0	1870	5.7	21.0	8.0	2150	283	50.0	285	142	3.4	—	—	—
1-26-56	220	77.8	1210	3.0	16.2	5.2	2150	299	48.4	276	—	—	—	—	—
1-27-56	68	—	920	0.0	15.9	3.9	2330	336	46.7	308	—	—	—	27	18
1-28-56	0	76.2	90	0.1	29.4	0.8	1878	136	40.0	239	126	3.3	86	27	26
1-29-56	2120	—	800	180.8	35.8	212.0	600	—	—	—	202	2.9	150	13	32
2-19-56	270	—	215	3.3	1.3	5.1	1300	174	14.8	156	126	2.5	90	17	43
2-24-56	340	—	850	23.9	4.1	47.1	1675	218	26.2	215	128	2.7	92	9	66

FIG. 2. Case 1. Microscopic appearance of villous papilloma. Component villi and glands are covered by a single layer of tall, columnar, mucus-secreting epithelial cells. The specimen was prepared with hematoxylin and eosin stain, × 97.

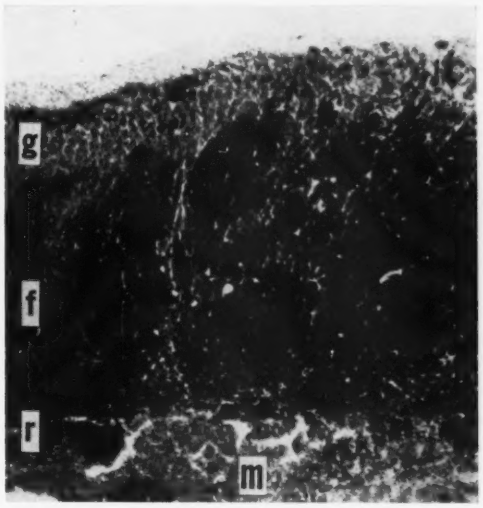

FIG. 3. Case 1. Frozen section of adrenal gland stained with Sudan black B. Note depletion of total lipids from zona glomerulosa (*g*). Zona fasciculata (*f*) and zona reticularis (*r*) contain a relatively normal distribution of lipids. Adrenal medulla (*m*). × 29.

2.9 milligrams, and 17-ketosteroids 9.1 milligrams per 24 hours. Values for serum sodium, potassium, chloride, and carbon dioxide, and for blood urea nitrogen are given in Table I.

The initial clinical impression was that the patient was suffering either from a salt losing nephritis or from adrenal cortical insufficiency. Consequently, a program of metabolic investigation was undertaken. The patient was given a diet calculated to contribute 1 gram of sodium chloride per day. This was supplemented by oral tablets of sodium chloride as required. Twenty-four hour collections of urine and of the watery rectal discharge were measured, and their sodium, potassium, and chloride contents determined. Water intake during the balance study was not directly supervised, but the fluid intake and output were measured and recorded. The serum electrolytes and the blood urea nitrogen levels were estimated at frequent intervals.

Over a controlled 8 day period, from 19 January to 26 January, she had a daily intake of 13 grams—220 milliequivalents—of sodium chloride. This was insufficient to maintain a positive salt balance as manifested by a progressive decline in concentrations of urinary sodium and chloride (Table I). The volume of the rectal discharge, i.e., 1,800 to 2,280 milliliters, and its sodium, potassium, and chloride content remained essentially unchanged.

On 27 January, the oral sodium chloride intake was restricted to 4 grams, or 68 milliequivalents, for the day. By that evening the patient complained of weakness, nausea, and vomiting. Her condition was not improved by the following morning and she complained of severe cramps in her thighs. Fluorohydrocortisone in a dose of 1.0 milligram was administered. Serum electrolytes were: sodium 126 milliequivalents, potassium 3.3 milliequivalents, and chloride 86 milliequivalents, per liter. That afternoon the patient became lethargic and drowsy. Nausea and vomiting continued and she had profuse sweating on even mild exertion. The blood pressure was 80 systolic, 50 diastolic. At 7:00 p.m. another 1.0 milligram of fluorohydrocortisone was administered. By midnight she appeared to be in circulatory collapse with a weak, rapid, irregular pulse and pallor. The urine volume for that day was 90 milliliters. She was given 1,800 milliliters of 5 per cent saline solution. There was some improvement in the pulse and blood pressure but the patient remained restless and apprehensive and continued to pass watery, mucoid fluid by rectum. Vomiting also recurred. She was then given 1,400 milliliters of 4 per cent sodium chloride intravenously in a period of 3 to 4 hours.

On 29 January, the patient was unresponsive and displayed generalized tremors. Serum electrolytes were repeated: sodium 202 milliequivalents, potassium 2.9 milliequivalents, and chloride 150 milliequivalents, per liter. It was believed that the patient's cerebral signs were at least in part due to hypernatremia with hyperosmolarity, and dextrose in water was administered in order to effect a dilution of extracellular electrolytes.

FIG. 4.

FIG. 4. Case 2. Barium enema illustrating irregular filling defect with cobblestone-like appearance in rectum and sigmoid colon (arrow).

FIG. 5. Case 2. Diagrammatic representation of technique used to cool villous tumor and reduce secretions preoperatively. Note continuous flow of ice water-alcohol mixture through rubber balloon placed in contact with tumor surface.

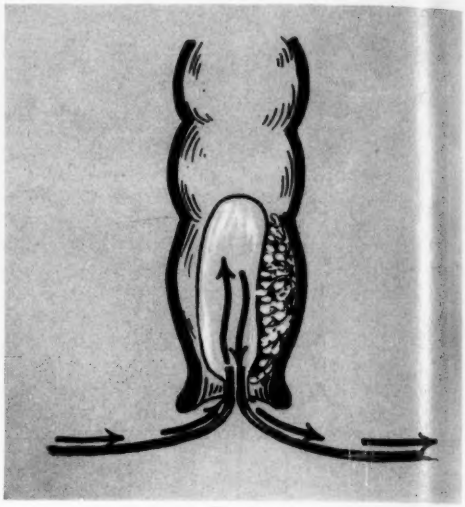

FIG. 5.

On 30 January, she began to respond to stimuli but continued to have generalized muscular twitching. Later that day she complained of thirst and was able to take fluids orally. There was some temporary clinical improvement for about a week and urinary output returned to 900 to 1,100 milliliters per 24 hours. Thereafter, anorexia, nausea, lethargy, and weakness developed, and the patient's condition progressively deteriorated. She complained of transient blindness and, at times, was mentally confused and depressed. In the face of depleted body stores of electrolytes and continued heavy daily losses in rectal discharge, complete electrolyte balance could not be achieved. She lapsed into stupor and died on 26 February 1956. Terminally, the blood urea nitrogen was 74 milligrams per 100 milliliters. The serum sodium was 104 milliequivalents, the potassium 3.4 milliequivalents, the chloride 95 milliequivalents, and the carbon dioxide 8.5 milliequivalents per liter. Death was attributed to electrolyte depletion with metabolic acidosis complicating a refractory diarrhea of undetermined cause. An intensive investigation of the gastrointestinal tract had been planned to follow the electrolyte balance study, but in view of the patient's debilitated condition during her last month of life and reports of previous negative findings elsewhere, this was abandoned.

TABLE II.—BIOCHEMICAL DATA IN CASE 2

Date	*Serum Na*	*Serum K, mEq./liter*	*Serum Cl*	CO_2	*B.U.N. mgm./100 ml.*
1– 7–60					72
1–11–60	139	2.9	87.5	32.2	51
1–13–60	132	2.6	83.3	29.5	77
1–14–60	133	2.2	98	21.5	61
1–15–60	135	2.4	92.9	21.6	52
1–16–60	131	2.7	97	19.5	47
1–18–60	133	3.7	95.6	27.1	28
1–20–60	134	4.2	99.0	27.0	36
1–21–60	135	4.5	98.3	27.6	33
1–25–60	140	5.0	103	24.7	16
2– 3–60	131	4.3	99	24.7	18
2– 5–60	132	3.7	96	23.7	—
2–12–60	138	4.4	105	24.0	13

At autopsy, a large villous papilloma composed of velvety folds of soft, pinkish-red tissue covered by innumerable filiform processes replaced normal rectal mucosa and encircled the upper rectal wall at a site 12 centimeters above the external anal sphincter (Fig. 1). The tumor measured 9 by 6 centimeters in surface dimensions and 2 centimeters in thickness. It was free of ulceration, was readily mobile over underlying muscle coats, and did not produce luminal obstruction. Distal to the villous lesion the rectum was dilated to about twice normal diameter and showed loss of mucosal pattern.

Microscopically, the rectal neoplasm was an adenoma composed of villi and glands covered by a single layer of tall, columnar, mucus-secreting epithelial cells (Fig. 2). Only a few small, focal areas of stratification of lining epithelial cells and intraglandular budding were encountered in the multiple step sections examined. There was no evidence of intraepithelial malignant change or of invasive carcinoma. Perirectal lymph nodes were negative for tumor cells.

Kidneys showed histologic features of mild senile nephrosclerosis. Bowie's stain failed to demonstrate granules in renal juxtaglomerular cells to advantage because of postmortem autolysis. Frozen sections of adrenal stained with Sudan III and Sudan black B dis-

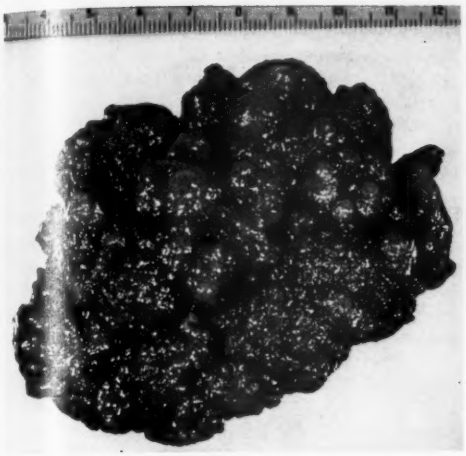

FIG. 6.

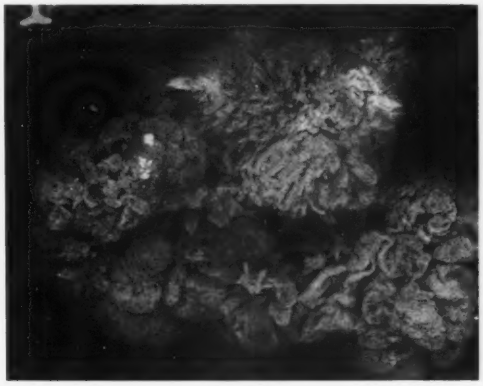

FIG. 7.

FIG. 6. Case 2. Gross specimen of villous tumor.

FIG. 7. Case 2. Tumor specimen photographed under water to display delicate frond-like processes harboring massive surface area.

closed depletion of total lipids from the zona glomerulosa (Fig. 3). There was no evidence of hyperplasia of this layer. The zona fasciculata and zona reticularis were essentially normal.

CASE 2. A 76 year old white male was admitted to the Surgical Service of the University of Alberta Hospital on 6 January 1960, complaining of diarrhea of 2 years' duration. The patient was a retired coal miner who had been well until the onset of a gradual change in bowel habit, characterized initially by episodes of frequent loose, watery bowel movements. These episodes had become increasingly severe and prolonged in duration, until during the month prior to admission his movements would be as frequent as 2 to 3 times per hour during the day, and several times during the night. It was apparent that these bowel movements consisted mainly of a profuse rectal discharge. There was no history of blood or pus in the stool.

The patient had lost 25 pounds in weight during the preceding year. His appetite, however, had not diminished, nor had there been any nausea, vomiting, or any abdominal pain. During the month prior to admission, he noticed increasing weakness, fatigue, loss of energy, and complained of excessive thirst associated with a dry tongue and lips.

Physical examination revealed an intelligent, cooperative, elderly male who did not appear acutely ill. There was no abdominal tenderness or palpable abdominal mass. Rectal examination disclosed a large, soft, cauliflower-like tumor involving the left lateral and posterior rectal walls. The upper limit of the lesion could not be reached with the examining finger.

Sigmoidoscopic examination on 7 January confirmed the presence of a large, fungoid tumor involving about one-half of the rectal wall and extending from the rectosigmoid region to within a few centimeters of the anal verge. Multiple biopsies were taken from this lesion.

The urine was clear, of acid reaction, and had a specific gravity of 1.013. Microscopic examination and tests for sugar and protein were negative. Hemoglobin was 17.9 grams, hematocrit was 55 per cent, and the white cell count was 12,400 with 68 per cent neutrophils, 2 per cent eosinophils, 23 per cent lymphocytes, and 7 per cent monocytes. A peripheral blood smear disclosed no cellular abnormalities. The erythrocyte sedimentation rate was 5 millimeters per hour. The serum albumin was 4.4 grams and the serum globulin 3.8 grams per 100 milliliters. The blood urea nitrogen was 72 milligrams per 100 milliliters.

An intravenous pyelogram on 10 January demonstrated no abnormality. A barium enema on 11 January outlined a large filling defect in the rectum and rectosigmoid regions, and several diverticula in the sigmoid colon (Fig. 4).

The pathologic report on the biopsy tissue described the lesion as a malignant villous papilloma of the rectum. On 11 January serum studies demonstrated a low potassium, hypochloremia and prerenal azotemia (Table II). Copious quantities of fluid, estimated at 1,000 to 2,000 milliliters per day, were lost in the rectal discharge. Accurate measurement of this loss was not possible because of rectal incontinence. The rectal fluid contained 110 milliequivalents of sodium, 38 milliequivalents of potassium, and 129 milliequivalents of chloride per liter.

A sulfathalidine and neomycin bowel preparation was initiated. Oral fluids were supplemented with intravenous therapy, including 1,000 milliliters of 5 per cent dextrose in distilled water on 11 January. On 12 January, he received 2,500 milliliters of fluid and electrolytes intravenously. On 13 January, he received

TABLE III.—PERTINENT DATA IN 18 CASES OF VILLOUS TUMOR WITH ELECTROLYTE DEPLETION

Case No. Author	Age, yrs. Sex	Duration of symptoms, yrs.	Site and size of tumor, cm.	Treatment	Result	Volume of rectal discharge, ml./24 hrs.	Blood urea nitrogen, mgm./100 ml.	Serum Na	Serum K mEq./liter	Serum Cl mEq./liter	Serum CO_2	Rectal discharge Na	Rectal discharge K mEq./liter	Rectal discharge Cl mEq./liter
1. McKittrick and Wheelock..	82 F	10	Rectum 8×14	Posterior excision	Recovery	375 to 2200	135	—	1.3	71	—	—	—	—
2. Fitzgerald.....	57 F	2	Rectosigmoid "large"	Anterior resection	Recovery	?	205	123	4.1	92	11.2	—	—	—
3. Starr and associates.....	82 M	3/52	Rectum and rectosigmoid "large"	Abdominoperineal resection	Recovery	1000 to 3000	21	132	2.7	100	21.4	—	80	—
4. Cooling and Marrack.....	43 F	13	Sigmoid colon 11×11	Left hemicolectomy	Recovery	2270 to 3400	97	120	2.2	80	27.0	122	25	—
5. Gutierrez Blanco—Case 1...	58 F	1	Rectum "size of orange"	Supportive and colostomy	Death	3000	150 to 210	—	—	—	—	—	—	—
6. Gutierrez Blanco—Case 2...	80 F	3	Rectum "large"	Supportive and electrocoagulation	Improved	3000	170	—	—	—	30.5	—	—	—
7. Goldgraber and Kirsner—Case 3.....	65 M	5	Rectum (recurrence?) 10×13	Abdominoperineal resection	Recovery	1300	82	137	4.1	100.3	29.6	123	—	117
8. Goldgraber and Kirsner*—Case 4.....	76 M	15	Rectum 13×10×5	Supportive	Death	?	172	102	4.4	65.6	9.9	—	—	—
9. Jordan and Erickson.....	59 M	5	Rectum 13×18	Abdominoperineal resection	Recovery	1500 to 2000	91	118	2.2	44.0	31.0	122	38.5	130
10. Roy and Ellis—Case 1.....	70 M	10	Rectum 4×5×10	Hartmann's operation	Recovery	?	152	115	3.2	70	—	122	28	112
11. Roy and Ellis—Case 2.....	56 F	5	Rectum 10	Anterior resection	Recovery	1500 to 2500	360	128	3.4	83	—	122	17.6	141
12. Mayfield and Milnor.....	57 F	10	Rectum and rectosigmoid "large"	Abdominoperineal resection	Recovery	1500 to 2000	181	101	2	58	—	158	43.5	—
13. Hoffman.....	63 M	"several"	Sigmoid and rectosigmoid 10×8	Anterior resection	Recovery	700 to 2500	116	119	3.4	78	—	151	15	140
14. Frye.....	63 M	1	Rectum and rectosigmoid 8×17	Anterior resection	Recovery	1000 to 2000	23	—	2.4	78	41	114	19	120
15. Walters and associates—Case 1	69 F	3/12	Sigmoid	"Resection"	Recovery	1000?	500	99	2.5	49	16	112	46	120
16. Walters and associates—Case 2	71 F	4/12	Rectum "size of tangerine"	"Local excision"	Recovery	Over 1000	120	132	2.8	96	—	103	40	99
17. Present report—Case 1.....	67 F	12	Rectum 9×6	Supportive	Death	600 to 2685	66	128	2.7	92	9	125	20	120
18. Present report—Case 2.....	76 M	2	Rectum and rectosigmoid 7×6	Posterior excision	Recovery	1000 to 2000	72	139	2.9	87.5	32.2	110	38	129

*Previously reported by Frazier.

3,000 milliliters of intravenous fluid, including 200 milliliters of hypertonic (5 per cent) saline and 80 milliequivalents of potassium chloride parenterally. Oral potassium chloride was also administered.

Despite this therapy, by 14 January the patient's clinical condition had deteriorated. Profound weakness, confusion, and marked dehydration were apparent. Lips and tongue were very dry, and loss of skin turgor was extreme. Copious loss of fluid continued from the rectal lesion, and the serum potassium steadily diminished in spite of the fluid and electrolyte replacement (Table II).

On 14 January, a decision was made to excise the rectal tumor. In an effort to diminish the rectal fluid loss, the tumor was cooled, using an ice water alcohol mixture which was flushed through a soft rubber balloon placed in the rectum (Fig. 5). This technique, modified from that described by Wangensteen and associates for gastric cooling, was not distressing to the patient and proved effective. During the 4 hours preoperatively that the apparatus was in use, the rectal discharge was virtually nil.

On the evening of 14 January, local excision of the rectal tumor was performed through a posterior approach. Bleeding was profuse and several transfusions were required. The operative area was packed open, and a loop sigmoid colostomy was performed. The patient responded well after this procedure. Fluid and electrolyte balance was rapidly restored and intravenous therapy was discontinued on the third postoperative day. By 20 January, the serum electrolytes were within normal limits, and by 25 January, the blood urea nitrogen had decreased to a normal level.

On 2 February, a posterior resection was performed, removing the entire rectum distal to the peritoneal reflection. The wound was again packed open. The postoperative course was entirely uneventful and the patient was discharged in satisfactory condition on 10 February 1960. He has remained well since discharge.

Histologic study of the original biopsy specimens showed the structure of a malignant villous papilloma of the rectum. The epithelial cells displayed disturbed polarity, deep staining nuclei, and frequent mitotic figures. Following excision, the tumor measured 7 by 6 by 3.5 centimeters. The gross appearance was of a soft friable papillomatous lesion (Fig. 6). Immersion under water demonstrated to advantage the delicate frond-like structure of the innumerable papillary projections covering the surface of the tumor (Fig. 7). Histologic sections revealed early invasion of the pedicle. After posterior resection of the rectum, multiple sections failed to reveal any evidence of residual tumor in the specimen or in regional lymph nodes.

DISCUSSION

Eighteen cases of villous tumor of the distal colon and rectum complicated by severe fluid and electrolyte imbalance have been collected for review (Table III), including 2 cases in the present report. This syndrome may be considered rare, judging from the infrequent report of cases, and the fact that none of the reviews of large series of villous tumors mention fluid loss to the point of electrolyte depletion and dehydration. In all probability, however, there have been other cases that have been unrecognized, unreported, or improperly classified.

CLINICAL FEATURES

Pertinent findings are summarized in Table III. There are 8 males and 10 females in this series—an almost equal distribution between the sexes. The average age is 66 years, the youngest 43 and the oldest 82. This mean age incidence is 2 years greater than that for villous tumors without electrolyte disturbances reported by Swinton and associates and can be explained by the fact that electrolyte depletion occurs as a late complication and is directly related to tumor size and surface area. The average duration of symptoms prior to severe electrolyte imbalance is about 5.4 years, as compared with an average duration of symptoms of 2.4 years to the time of diagnosis and treatment in a series of villous tumors without electrolyte imbalance reported by Sunderland and Binkley.

The characteristic symptom of a villous tumor of the colon is a copious mucus discharge from the rectum. This results in a "pseudodiarrhea" which may vary from an occasional simple passage of mucus to an elimination of 5 to 20 watery or mucous stools a day. Frequently the diarrhea is most severe in the early morning because of an accumulation of mucous secretion in the rectum during the sleeping hours. Initially, episodes of refractory mucous diarrhea last for only a few days at a time and occur at irregular intervals separated by several weeks or months. Eventually, the rectal discharge tends to become almost continuous with fluid losses ranging from 375 to 3,400 milliliters per 24 hours. The volume of loss is underestimated unless accurately measured.

*Previously reported by Frazier.

Patients with villous tumors complicated by fluid and electrolyte imbalance either present as an emergency or culminate in an emergency. The onset of ill health is often heralded by gastrointestinal symptoms superimposed on a long standing mucous "pseudodiarrhea." Vague abdominal pain, anorexia, weight loss, excessive thirst, nausea, and vomiting may be present for several days or a few weeks, preceding total collapse. Those who are seen as an emergency usually have failed to seek early medical advice or have refused adequate treatment and suffer a recurrence of tumor after attempts at palliation or cure. Nine patients were dangerously ill or moribund when first brought to the hospital, and in 8 of the remainder signs and symptoms of severe fluid and electrolyte depletion developed during one or more stages of their illness. These patients displayed marked dehydration, lethargy, weakness, oliguria, acidotic breathing, mental confusion, and hypotension. If a history of diarrhea is not available, this clinical picture may be confused with diabetic coma, adrenal insufficiency, or other causes of sudden collapse.

Other symptoms include rectal bleeding, change in bowel habit, tenesmus, prolapse of the tumor, and elimination of tissue particles. Gross bleeding was noted in only 3 patients in the present series. In contrast, 45 of 50 patients in the study by Wheat and Ackerman had symptoms of rectal bleeding.

PATHOPHYSIOLOGY

Several interesting aspects of the pathophysiology of fluid and electrolyte loss from a villous tumor of the distal colon warrant emphasis. It seems likely that this syndrome is a potential complication in any patient with a large villous tumor who loses a liter or more of fluid from the rectum per day. In such a patient, adequate oral intake of salt and water may serve to maintain a delicate fluid and electrolyte balance. A borderline or deficient state may remain asymptomatic and unrecognized for a long time unless detected by biochemical studies. Knowledge of electrolyte imbalance in their first patient prompted Walters and associates to carry out biochemical examinations in their second patient who was clinically well. The serum sodium was 132, serum potassium 2.8, and serum chloride 96 milliequivalents per liter. These were corrected preoperatively. Hoffman has emphasized that operation upon a patient with unsuspected fluid and electrolyte depletion may prove lethal.

The dietary intake of water and electrolytes in these patients must fall below some critical level before abnormal losses will produce clinical effects of deficiency. In our first case, large fecal losses of water and salt were compensated over many months by a very high dietary intake, 16 to 18 glasses of water and 15 to 20 grams of sodium chloride daily. Clinical signs of sodium deficiency appeared when the oral intake of salt was reduced to 13 grams—220 milliequivalents—per day for 8 days. Decreased oral intake or increased rectal fluid loss may thus upset biochemical balance and precipitate a state of acute fluid and electrolyte depletion. Acute deficiency may also be provoked by irregular food intake occasioned by nausea or vomiting, added losses through perspiration during hot summer weather, or by routine fluid restriction associated with investigative laboratory or roentgenologic procedures in the hospital. In some instances, temporary restoration of the tenuous balance may be achieved by active administration of fluids and electrolytes. This phenomenon was observed in a number of patients in this series whose villous tumors were unrecognized, untreated, or inadequately treated initially and recurred. These patients had fluid and electrolyte deficiencies which were corrected but they invariably returned after varying intervals with a recurrence of the depletion syndrome.

All patients in this series were observed either initially or ultimately with evidence of severe fluid and electrolyte depletion. Pertinent biochemical data are given in Table III. Laboratory findings include hypokalemia, hyponatremia, hypochloremia,

azotemia, acidosis, decreased plasma carbon dioxide content, and hemoconcentration. When first seen, some patients have, in particular, deficiencies in potassium while others are mainly deficient in sodium. These differences are probably related in part to variations in dietary intake of sodium and potassium, and in part to differences in potassium concentration in diarrheal fluid from one case to another. Sodium ranges from 103 to 158, potassium from 15 to 80, and chloride from 99 to 141 milliequivalents per liter in the rectal fluid. The normal subject passes 100 to 200 milliliters of water per day in his stools with 2 to 5 milliequivalents of sodium and 10 to 15 milliequivalents of potassium. The losses in the villous tumor syndrome, therefore, represent a 10 to 40 fold increase over normal values.

If the diarrhea fluid were a simple transudate, the ratio of potassium to sodium should be comparable with that of the blood serum. However, potassium concentration in the rectal fluid averages 13.2 times the concentration of that in the serum. Sodium and chloride levels in the rectal fluid generally approximate those in the blood serum. Recently, Roy and Ellis have studied secretions aspirated directly from the surface of 2 villous tumors of the colon. In neither patient was there any evidence of disturbance of serum electrolytes. In the first patient, the fluid contained 96 milliequivalents of sodium, 54 milliequivalents of potassium, and 114 milliequivalents of chloride per liter. In the second patient, the fluid contained 282 milliequivalents of sodium, 98 milliequivalents of potassium, and 538 milliequivalents of chloride per liter. These findings suggest that there may be an active secretion of potassium by the cells of villous tumors.

Potassium depletion through fecal loss may occur in a variety of severe diarrheal states, including ulcerative colitis, regional enteritis, cholera, bacillary dysentery, Whipple's disease, malabsorption syndrome, islet cell tumor with refractory diarrhea, and chronic purgation. Normal bowel secretions are rich in potassium; an average potassium level of large bowel contents obtained by cecostomy is 20.6 milliequivalents per liter, with a high of 47.3 milliequivalents per liter. It is therefore possible that potassium loss in the villous tumor syndrome is only the quantitative result of potassium-rich mucous secretion from the vast surface area of the tumor.

It is possible that the composition of fluid secreted from a villous tumor may be altered to some extent prior to its discharge through the rectum as a result of selective reabsorption by colonic epithelium. Effectiveness of reabsorption would depend upon the site of the tumor, and the duration of fluid contact with absorptive colonic epithelium. Cooperstein and Brockman have demonstrated active sodium absorption and bicarbonate secretion across the colonic mucosa associated with an electrical potential gradient of 10 to 40 millivolts. Concurrently, potassium is transferred from the blood to the lumen, in the direction of its electrical gradient but opposite to its chemical gradient. Net water flow depends on the degree of active transport of sodium, bicarbonate, or both. The absorption of chloride is in the direction of its electrochemical gradient, probably modified by net water movement.

Sodium deficiency may be illustrated by referral to Table I. This patient went into negative electrolyte balance over a 10 day period while receiving 220 milliequivalents of sodium chloride orally per day for 8 days, 68 milliequivalents on the ninth day, and 0.0 milliequivalents on the tenth day. During this interval, the 24 hour urine sodium content declined from 81.3 to 0.1 milliequivalents. Concurrently, the daily loss of sodium ion in rectal fluid fluctuated between 208 and 386 milliequivalents, and only dropped to 136 milliequivalents when there was a proportional decline in serum sodium concentration to 126 milliequivalents per liter on the last day of salt deprivation. A similar pattern was noted with urinary, fecal, and serum chloride levels. The fact that urine values for sodium and chloride approached minimum possible levels pre-

cluded electrolyte loss from either renal or steroid disorders. Renal conservation of sodium is mediated largely through the adrenal cortex and particularly through the release of aldosterone. The regulation of water excretion is under the control of the posterior pituitary hypothalamic system through the secretion of antidiuretic hormone, which in turn exerts its effect by modifying the permeability of the distal renal tubules to water. From the data presented, it is evident that the sodium and water content of diarrheal fluid was unaffected by homeostatic control mechanisms but declined only when there was a fall in serum sodium concentration and in blood pressure.

Morphologic alterations relating to chronic sodium depletion were sought in adrenals and kidneys in our first patient. Adrenal glands displayed loss of total lipids from the zona glomerulosa, the pattern closely resembling that found by Nichols in hypertensive patients on a low sodium diet. The change appears to correlate with an elaboration and release of aldosterone in response to sodium depletion. Pitcock and Hartroft have noted increased granulation of the juxtaglomerular apparatus of the kidney in association with hyponatremia. This feature could not be adequately assessed in our case because of blurring of cytologic detail in juxtaglomerular cells due to postmortem autolysis. Lesions of chronic potassium deficiency, i.e., vacuolar nephropathy and focal myocardial necrosis, were not encountered in either of our patients.

A marked elevation of the blood urea nitrogen was a prominent finding in most patients in this series. This azotemia is prerenal in origin and is reversible. It is best explained by the effect of reduced blood volume and hypotension on renal blood flow and glomerular filtration. In the absence of concomitant renal disease, urinalysis reveals a high specific gravity and reduced concentrations of chloride, sodium, and/or potassium. Reduction of the elevated urea nitrogen levels occurs rapidly after correction of the dehydration, hypovolemia and electrolyte imbalance, and resection of the offending lesion.

A metabolic acidosis associated with a decreased plasma carbon dioxide content was observed in almost all patients. This acidosis appears to be due both to prerenal uremia with retention of acid metabolites and to excess loss of cations over anions in the diarrheal fluid. On the other hand, metabolic alkalosis was recorded by Frye in a patient with low serum chloride, low serum potassium, normal blood urea nitrogen levels, and a high carbon dioxide content.

Hemoconcentration is a reflection of dehydration and hypovolemia as a result of water loss from the rectal discharge. Losses as great as 3,400 milliliters of fluid per day are noted. The volume of mucous secretion relates directly to the surface area of the growth, and the villous tumors in this series were all of large size. The quantity of secretion does not appear to be affected by malignant change.

Histologically, the structure of this lesion is identical with that of the usual papillary tumor of the rectum. Malignancy of varying degree is a common complication of villous tumors. Wheat and Ackerman state that 76 per cent of the tumors in their series showed either focal atypical changes, focal carcinoma, or frank invasive carcinoma. Similar histologic findings were observed in 10 patients, 55 per cent, in the present series. A small focus of malignant degeneration in a large villous tumor may be obscured by overhanging villi, missed on biopsy, and remain unsuspected unless multiple sections from the entire lesion are carefully examined following removal. In 4 patients in the present series, malignancy within the villous tumor was not demonstrated on biopsy, but was found on later examination.

DIAGNOSIS

In all reported cases of villous tumors with fluid and electrolyte imbalance, the tumor has been situated in the rectum or sigmoid colon, within reach of the examining finger or of the sigmoidoscope. Despite the acces-

sibility of the tumor and the invariable large size of the lesion in this syndrome, there may be difficulty in establishing the diagnosis. Gabriel has emphasized the soft impalpable nature of large villous tumors which may readily evade detection on rectal examination. The pale, unresisting growth may also be passed over by the sigmoidoscope and repeated, careful examinations may be required to ascertain the presence of a villous tumor.

Barium enema studies are of aid in outlining the extent of large growths in the proximal rectum and distal colon. Frye believes that the roentgenologic findings of a large mass showing linear streaks of barium extending into it, and feathery margins on the postevacuation films may be characteristic features of villous tumors. A somewhat similar manifestation is apparent in our second patient on the barium enema which demonstrates a filling defect with a rather unusual cobblestone-like appearance seen in Figure 4.

Diagnosis of a villous tumor may be suspected by the gross appearance of the lesion but must be confirmed by histologic section. Multiple biopsies should be taken, searching for suspicious areas of induration or ulceration, in an attempt to gain an over-all picture of the tumor and to reveal occult malignancy.

Early diagnosis is essential for the patient with a villous tumor complicated by fluid and electrolyte imbalance if the syndrome is to be managed successfully. In 16 patients in this series, the villous tumor was discovered by digital rectal examination or sigmoidoscopy. In 2 patients, the diagnosis was missed and the villous tumors were identified at autopsy. Immediate implication of the gastrointestinal tract as the site of an offending lesion is obvious in the patient whose primary complaint is of a refractory mucous or watery rectal discharge. The significance of the colon and rectum, however, may be overlooked in patients who have a clinical picture of profound fluid and electrolyte depletion, or complete collapse. Villous tumors must be considered in the differential diagnosis of these patients, and investigation of the lower part of the bowel should not be unduly delayed.

A state of fluid and electrolyte depletion may be suspected from clinical symptoms and signs and may be confirmed by laboratory examinations. An occult deficiency syndrome was detected in 1 patient (Case 16) in the series who appeared completely well clinically. Serum electrolyte and blood urea nitrogen determinations should, therefore, be performed in all patients with villous tumors of the large bowel in whom there is any appreciable fluid loss from the rectum.

TREATMENT

Treatment of patients with villous tumors complicated by fluid and electrolyte imbalance involves correction of the depletion syndrome and removal of the lesion. Severely ill patients require immediate therapy with parenteral fluids containing sodium, potassium, and chloride ions in amounts sufficient to correct existing deficits. Large quantities of fluid and electrolytes are often required. Intravenous doses up to 200 milliequivalents of potassium daily have been required to correct and maintain potassium levels. Cautious administration of hypertonic saline may be of value in rapid correction of a hyponatremic state.

Rectal loss is invariably underestimated. Accurate measurement of the quantity and electrolyte content of the rectal fluid is a valuable guide to replacement therapy. If severe diarrhea persists, the response to treatment may be slow or unsatisfactory. In these patients, early diagnosis of the villous tumor and recognition of the potentially lethal nature of the associated biochemical disturbance is of paramount importance. Three fatalities occurred in this series of 18 cases, and all 3 patients died of fluid and electrolyte depletion despite replacement therapy. In 2 of these patients, the tumor was unrecognized until autopsy. In the third patient, colostomy without resection of the lesion was of no avail.

Antidiarrheic medications are ineffectual in the control of rectal discharge from this tumor. Wangensteen and associates have recently emphasized that local cooling diminishes gastrointestinal tract secretions, and in our second patient, local hypothermia was used (Fig. 5). For an admittedly short interval we found this measure to be effective in reducing secretion from the tumor.

Ideally, correction of the fluid and electrolyte imbalance should be achieved before surgical removal of the tumor is undertaken. This may not be possible. In the face of a profuse and intractable rectal discharge, resection of the lesion is the only definitive therapy and may have to be performed as an emergent procedure before fluid and electrolyte balance has been completely restored. In at least 5 patients in this series, normal fluid balance, reduction of the blood urea nitrogen, and restoration of normal serum electrolyte values could not be achieved before surgical resection was performed (Table III, Cases 4, 11, 12, 15, and 18). It is possible, but far from certain, that more intensive fluid and electrolyte replacement could have restored normal biochemical balance in these patients preoperatively.

Adequate local excision is the treatment of choice for villous tumors of the large bowel. Adequate local excision means removal of the entire villous tumor in one piece, including the stalk, and a margin of normal tissue on all sides including depth. Villous tumors associated with fluid and electrolyte depletion are invariably very large lesions because of the extensive surface required to secrete sufficient fluid to disturb the homeostatic state. Such a lesion usually requires an extensive bowel resection to effect an "adequate local excision."

Appropriate bowel resection, including anterior resection, posterior excision, or an abdominoperineal resection, was performed in 14 patients in this series with satisfactory results. Two patients in whom surgery was not performed died of fluid and electrolyte imbalance (Table III, Cases 8 and 17). Diversionary colostomy to reduce rectal discharge proved ineffective in another patient and death ensued (Table III, Case 5). Resection was considered too formidable in one patient, and improvement followed electrocoagulation of the lesion (Table III, Case 6).

The treatment of villous tumors by fulguration, irradiation, or inadequate local excision is unsatisfactory and is followed by a high recurrence rate. Twenty-five electrodesiccations of a villous tumor over a 2 year period in the patient described by McKittrick and associates were followed by recurrence. This patient finally consented to posterior excision of the rectum. Jordan and Erickson reported a case in which surgical treatment was initially refused and radium mold treatment was performed. The lesion recurred with fluid and electrolyte imbalance, and an abdominoperineal resection was finally carried out.

If malignancy is found in a villous tumor, the appropriate cancer operation should be performed. Knowledge that a potentially lethal state of fluid and electrolyte loss can occur with villous tumors of the distal bowel should serve to increase early recognition and definitive therapy.

SUMMARY AND CONCLUSIONS

1. Certain villous tumors of the large bowel characterized by a copious mucous or watery rectal discharge may produce a syndrome of severe fluid and electrolyte depletion.

2. Case studies of 2 patients with this syndrome have been presented, and 16 other similar cases have been collected from the literature and reviewed.

3. These patients either are emergency cases or culminate as emergencies. Dehydration, hypokalemia, hyponatremia, hypochloremia, prerenal azotemia, and circulatory collapse are the characteristic clinical and biochemical features.

4. Death from fluid and electrolyte imbalance occurred in 3 cases. Successful management requires early diagnosis of the tumor, restoration of fluid and electrolyte balance, and surgical removal of the lesion.

Appropriate resection of the involved bowel is the procedure of choice to effect adequate removal of large villous tumors of the rectum or rectosigmoid complicated by fluid and electrolyte loss.

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CLOSED CHEST CARDIAC RESUSCITATION

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THE RECENT DESCRIPTION by Kouwenhoven, Knickerbocker, and Jude of closed chest cardiac resuscitation marks an important contribution to the treatment of circulatory arrest. The work represents a happy union of chance observation and prepared mind. Kouwenhoven and Knickerbocker were seeking a means to keep animals alive long enough during ventricular fibrillation to test various methods of external electrical defibrillation. They discovered that pressure on the animal's chest with the heavy external electrodes gave an arterial pressure pulse and that rhythmic pressure resulted in maintenance of the peripheral circulation and prolongation of the viable period. Subsequent use of this method on patients by Jude showed that it was effective not only on children, as had been anticipated, but also on adults. In fact in several documented instances better circulation could be maintained in the closed chest than when it was open.

Effective closed chest cardiac resuscitation depends upon entrapment of the heart between the sternum in front and the vertebral column behind. The thoracic cage in unconscious and anesthetized patients may be surprisingly mobile. Thus blood is forced out of the heart by pressure on the sternum, and the heart refills during relaxation. In practice it is helpful to have the patient on a rigid support such as a stretcher, the floor, or a board placed under him if massage is to be given in a soft bed. The heel of one hand with the other on top of it is placed on the sternum just cephalad to the xiphoid. Firm, quick pressure is applied vertically downward about 60 times per minute, and at the end of each pressure stroke the hands are lifted to permit full expansion of the chest. The operator should be positioned directly over the patient in order to be most efficient in his efforts. If possible someone should feel the femoral or other pulse, and if this is not forceful the location of the operator's hand or his manner of applying pressure should be altered. A quick, forceful pressure is important. Some pulmonary ventilation is provided by the closed chest massage, and if there is only one person present, attention should be concentrated on the massage. If there are more persons available, one should massage the heart while another ventilates the lungs by mouth-to-mouth or other available means.

Surgeons have been slow to accept the value of massage applied through the chest, being conditioned to the urgency of opening the thorax and massaging the heart within minutes of onset of circulatory arrest. When given a fair trial, however, external massage compares favorably with that given with the open chest. Either may be ineffective if the operator is not sensitive to the fact that small changes in the position and manner of pressure may make large differences in the peripheral pulse obtained. The pulse felt in the femoral, carotid, or brachial areas should be the guide to change in technique, and if this is satisfactory with external massage the chest need not be opened. Ex-

ternal massage is the method usually used at the Johns Hopkins Hospital in the treatment of cardiac arrest and only rarely is the chest opened. The effectiveness of this method has been documented many times by direct measurement of arterial pressure and by survival of patients.

External cardiac resuscitation may be lifesaving in the patient who has circulatory arrest outside the hospital. A recent case documents this statement: The patient had been followed in the cardiac clinic because of myocardial infarction and associated electrocardiographic abnormalities. He and his family were aware of the threat of sudden death and so when he fell unconscious at dinner an ambulance was immediately called. The ambulance driver had, during the preceding week, attended a class given by Kouwenhoven on external massage and he performed this while his assistant used mouth-to-mouth ventilation until the patient could be transported to the ambulance and a respirator. External massage was continued in the ambulance and later, for 10 minutes, in the hospital where ventricular fibrillation was confirmed electrocardiographically and external defibrillation accomplished. The patient convalesced normally from a myocardial infarction which had apparently triggered the arrhythmia. The minimum time from apparent death to arrival in the hospital was 20 minutes. Open cardiac massage would have been virtually impossible under such circumstances.

The value of external massage lies in its simplicity. No ventilating equipment—other than mouth-to-mouth ventilation—intratracheal tube, or surgical instruments are needed. No incision is made and there is none to close, a valuable saving of time, discomfort, and life. More important, however, is the fact that since there is no disfigurement of the patient, or the surroundings, there should be less hesitation in starting massage, and the golden first few moments need not be spent in deliberation as to whether or not the effort should be made.

In some instances the heart will be fibrillating, or if there is asystole it may begin to fibrillate after circulation is restored, and electrical defibrillation must be accomplished. An external defibrillator is then necessary, but, just as when the chest is opened, circulation can be kept up while equipment is brought for external defibrillation.

Closed chest cardiac resuscitation will result in the saving of many lives.

THE ROLE OF ELECTRICAL PACEMAKERS IN THE TREATMENT OF UNEXPECTED CARDIAC ARREST

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DURING THE PAST 8 YEARS cardiac pacemakers have found an important use in the immediate and prolonged treatment of postoperative or spontaneously occurring heart block in which the idioventricular rate has become too slow to provide adequate cardiac output. Scarcely a major hospital in the country lacks one of these electronic devices. For the treatment of Stokes-Adams disease with heart block the role of pacemaker therapy is well established, but in other situations the popularity of pacemakers has sometimes outstripped their value. Ill-conceived efforts at cardiac stimulation can result in deaths either by direct injury or because the effort at pacemaking supplants more effective means of therapy. The commonest of these abuses have occurred in the treatment of patients with cardiac arrest.

Some patients with cardiac arrest have been resuscitated with pacemaker therapy. This group of patients should serve as a guide in determining the limitations and indications for electrical stimulation in cardiac arrest. In virtually all successful cases the possibility of cardiac arrest was recognized in advance, either because of preexisting abnormalities such as heart block or because of capricious behavior of the heart under anesthesia. Because of the advance warning, the pacemaker was available at the patient's side and often the electrodes were in position on the chest. When arrest occurred, stimulation was immediately performed. Pacemaking warranted a trial under these circumstances both because this is the time when stimulation is most apt to succeed and because its use if unsuccessful would not materially delay the institution of some form of cardiac massage.

If pacemaker therapy cannot be immediately applied, it is likely to fail even in the most favorable cases. The capacity for electrically evoked contraction decreases with every second of continued asystole so that in 2 or 3 minutes an unresponsive myocardium develops in a favorable candidate for stimulation. In other cases, the assumption that cardiac arrest is due purely to failure of the conduction system may not be warranted. Almost invariably the arrest is the final result of a bout of anoxia and hypercapnia in which the myocardium has also been damaged. In other instances, fibrillation may have occurred, or a heart beat may be present but so feeble that no blood pressure is obtainable. When cardiac arrest is announced, the patient's chance for prompt massage may be delayed by frantic and time-consuming efforts to procure and apply a pacemaker. When electrical stimulation is finally begun in such patients with unexpected arrest, the myocardium will usually be incapable of contraction.

The primary emphasis in the therapy of unexpected cardiac arrest should still be on cardiac massage, carried out directly or conceivably by the recently described method of external compression. If electrical pacemaking is to be tried, it should be under circumstances which will not significantly delay the application of standard methods of treatment.

THE SURGEON AT WORK

DETERMINATION OF THE VASCULAR STATUS OF PEDICLE SKIN GRAFTS BY RADIOACTIVE TRACER STUDIES

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THERE IS NEED FOR A METHOD to determine accurately the viability of flap and tube pedicle skin grafts. In the past, the decision to sever a pedicle from its donor blood supply has been based upon the normal time of healing. This norm represented experience acceptable in approximately 85 per cent of cases, but the usual range of acceptable times was from 18 days to 5 weeks.

Uncertainty as to the exact time that a pedicle can be cut from its original blood supply may result in an unnecessarily prolonged period of hospitalization which is an inconvenience and an expense to the patient. Severance of the pedicle at 3 weeks, for example, is premature in some instances and leads to the complication of necrosis; but also 3 weeks is probably a little too long in most instances. Therefore, precise knowledge of the vascular readiness for severance could be extremely valuable. According to Barron and Veall, an average of from 7 to 10 days of hospitalization may be saved. Our interest has focused primarily on the avoidance of cutting pedicles too soon.

In attempts to determine accurately the vascular status of pedicle skin grafts, several tests have been introduced. One of the easiest is the observation of the color and temperature of the pedicle when compression occludes circulation. However, the changes may be slight and difficult to evaluate. Hynes (4, 5) described two other methods. First, a fluorescein test was made more accurate by utilizing histamine wheals to sharpen the end-point; and second, an atropine test was introduced to determine the end-point by recording the rise in pulse rate, dryness of the mouth, and patient's inability to read. When several investigators—notably Barron and Veall (1, 2) and Kety—introduced radioactive electrolytes to determine the source of the pedicle graft's blood supply, crude measures were no longer necessary. We have modified these tests to fit our needs and have applied them to patients with reproducible results.

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METHODS

Both radioactive sodium chloride and radioactive sodium iodide have been employed in our cases, but recently the latter has been used exclusively because it is so readily available. A dose of about 1 microcurie in 0.1 milliliter of solution is injected into the most superficial subcutaneous tissues in the center of the pedicle or flap. The site is marked with an indelible pencil so that it may be used in future tests.

Ideally, the radioactivity is measured with a collimated, movable scintillation counter with

TABLE I.—SUMMARY OF CASES

Case No.	Age Sex	Diagnosis	Site of skin graft: Recipient	Site of skin graft: Donor	Postoperative test: Day	Postoperative test: Per cent block	Postoperative severing of pedicle: Day	Postoperative severing of pedicle: Result
1	31 M	Compound comminuted fracture, l. tibia and fibula	Lateral aspect, l. leg	R. thigh	17	0	21	Complete survival
2	35 M	Compound comminuted fracture, l. tibia and fibula, with secondary traumatic ulcer	Anterior aspect, l. leg	R. calf	19	0	21	Complete survival
3	24 M	Infected fracture, l. tibia	Anterior aspect, l. leg	R. calf	21	0	½ 23 ½ 25	Complete survival
4	55 M	Rheumatoid arthritis with thermal burns, both hands and legs	L. hand	Abdomen	11 18 21 26	75	26	Necrosis of tip of graft
			R. hand	Abdomen	18	0	30	Complete survival
5	31 M	Cornpicker injury with amputation of all fingers of r. hand	R. hand	Abdomen	12	0	16	Complete survival
6	16 M	Actinodermatitis with ulceration of dorsum of l. hand and necrosis of metacarpals	L. hand	Abdomen	16 21 28 33	63 50 35 22	35	Complete survival
7	45 M	Avulsion and crushing injury to r. hand	R. hand	Abdomen	11 17	58 18	18	Necrosis of proximal ⅙ of graft

a logarithmic readout. An apparatus with arithmetic readout is used and the results are plotted on semilog paper. The crystal of the counter is collimated for 13 centimeters with about 2 to 3 centimeters of working distance between the instrument and the skin. A desirable initial reading is about 400 to 500 net counts per second.

With the counter in place, the injection is made and continuous readings are taken. The points are plotted on semilog paper at 1 minute intervals. At the end of 10 minutes the donor end of the pedicle flap is occluded with a pair of rubbershod Steinmann pins under pressure of rubber bands. The counts are recorded for 10 minutes while the circulation is occluded, and for another 10 minutes after the clamps are released. At all times the graft is carefully observed for leakage of solution from the puncture wound onto the skin; if this occurs, it is blotted away. Also, the graft is observed for cyanosis and other signs of ischemia

A typical two component disappearance curve is shown in Figure 1, which is a logarithmic plot of the disappearance of radioactive sodium iodide from a graft that was not clamped. The terminal portion of the curve which is represented by a straight line on the logarithmic plot is extrapolated back to the vertical axis and the superimposed fast component, important during the first 10 minutes, is subtracted from it and plotted as shown.

It should be noted that the 10 to 20 minute segment is fairly straight, although the rate is still a little faster than is that of the 20 to 30 minute segment.

Of course, since a clamp normally is applied during the 10 to 20 minute period, the rate of iodide disappearance that would have obtained without clamping (Rb) must be estimated. The actual disappearance rate (Rc) during this period of clamping is determined. Then the ratio Rc/Rb, multiplied by 100, expresses the actual flow from the recipient site during occlusion as a percentage of normal flow. The percentage block may be calculated by subtracting percentage flow from 100.

RESULTS

Our experience with this method has been with 15 flow rate determinations in 7 patients and is summarized in Table I. In no instance

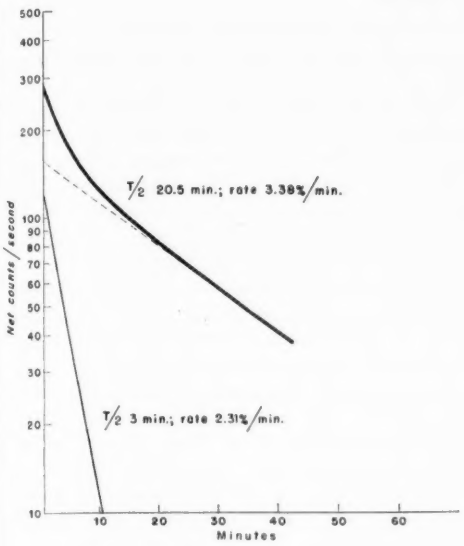

FIG. 1.

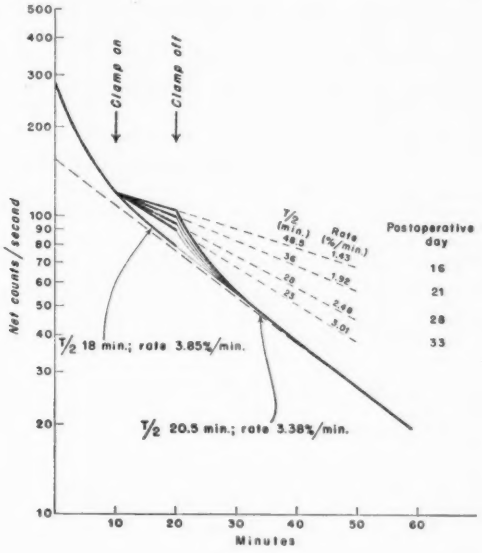

FIG. 2.

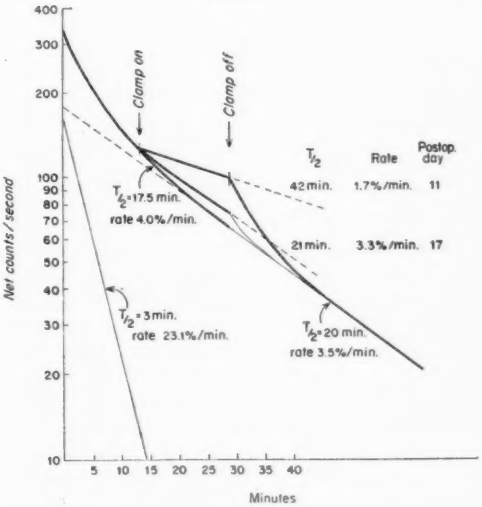

FIG. 3.

FIG. 1. Case 6. Typical radioactive electrolyte—sodium iodide—disappearance curve plotted from test of skin graft pedicle not clamped. Note two exponential disappearance rates.

FIG. 2. Case 6. Composite of radioactive electrolyte—sodium iodide—disappearance curves. Block, evident during clamping, decreased gradually through course of study.

FIG. 3. Case 7. Composite of radioactive electrolyte disappearance curves. Block, evident during clamping, decreased rather rapidly between the 2 tests.

was the injury limited to the skin, and consequently all patients required multiple procedures to restore function in addition to replacement of extensive loss of skin. Most of the patients had traumatic lesions, but as shown in the Table I, 1 patient with rheumatoid arthritis had sustained a thermal burn, and another patient, as a youth, had received radiation therapy for warts and subsequently had had severe actinodermatitis.

The cases can be divided into 2 groups. Tests were not made in Cases 1 through 5 until it was considered time to sever the pedicle. Among these 5 cases the isotope studies of 6 grafts confirmed the adequacy of the blood supply from the host tissues in 5, and after the pedicles were severed, uncomplicated healing resulted in these 5 instances. In the other instance, Case 4, the percentage block was 75 per cent, but because of the patient's bitter complaints it was decided to sever the pedicle 26 days after transfer. A corner of the detached pedicle, comprising about one-sixth of the graft, was lost.

The second group, Cases 6 and 7, was studied more recently and these were the first in which the gradual drop in the percentage block was watched closely.

In Case 6 (Fig. 2), the damage to the tissues receiving the graft had been severe, and their

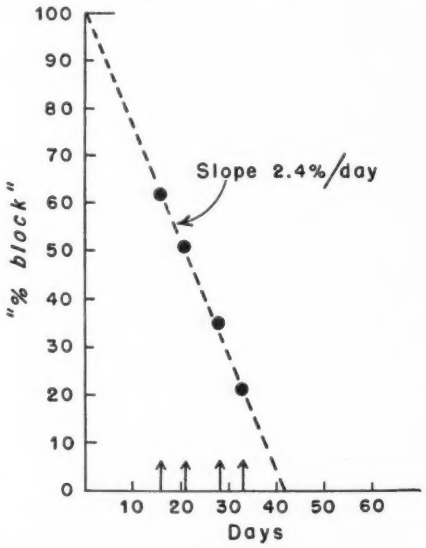

FIG. 4. Case 6. Plot of diminution of vascular block with time.

vascularity left much to be desired. This was evident from comparison of the lengthy period required for decrease of the percentage block in this case with the shorter corresponding period in Case 5, in which the recipient site was highly vascular.

Possibly, in Case 7 not all circulation through the donor end of the graft was occluded when compression was applied during the last isotope study, and a false reading (Fig. 3) was thus obtained. Or, more likely, it may be that too much of the adherent graft was mobilized at the last surgical procedure; for if so, this could explain the inadequacy of the blood supply which resulted in necrosis of a portion of the graft.

In Cases 5 and 7, the radioisotopic determination of adequacy of vascular supply to the transplanted pedicle grafts shortened the hospital stay.

Although in some of these cases the hospital stay was not shortened, the patient's and surgeon's confidence was greatly increased. In the future, we believe, the technique described will make possible the selection of an increasing number of patients having enough blood supply from the recipient site for detachment of the pedicle in less than the traditional period of 21 days.

COMMENT

The plots show plainly whether there is a decreased rate of outflow of the isotope from the graft. A question to be answered is, how much compromise of flow is compatible with viability of the pedicle after the donor blood supply is ended. We have sought to do this by comparing the rate in the clamped area with the rate that would have obtained had the pedicle not been clamped and have called this the ratio percentage flow. We hope that this or its complement, the percentage block, will prove consistent from patient to patient and will indicate the lower limits of block that a graft will tolerate when it is detached.

Goetz stated that only 10 per cent of the circulation to the skin is necessary for nutrition, the function of the other 90 per cent being part of the body's heat regulating mechanism. If this is true, then the percentage block at which the pedicle can be divided safely is somewhat greater than that which we have used.

In Case 6, we observed a gradual arithmetic diminution in the percentage block (Fig. 4). This curve is probably a function of a healing rate of 2.4 per cent per day.

One of the variables in the clamping technique used has stemmed from lack of precise determination of pressure exerted by the clamped Steinmann pins. Great care must be maintained to assure that there is no leakage under the clamp, which is what may have happened in Case 7. Now a controlled method has been devised for compressing the pedicle. A sphygmomanometer pressure bag has been fitted under the Steinmann pins. This bag can be put in a sterile covering and positioned at the beginning of the test before the radioactive material is injected. Steinmann pins, bars, or rods may be loosely applied over it and fixed in place. When it is desired to clamp the pedicle, one has only to inflate the bag to a pressure just in excess of the systolic blood pressure.

It should be noted that this test measures outflow from the pedicle graft as it is when the clamps are on: it cannot be expected to measure flow after any surgical revision or undermining, such as may occur when the pedicle is severed and revised for neat closure of the defect. Elevation for such revision should be postponed until it is certain that the circulation in the graft is maximal, and such postponement may extend to several months.

Barron and associates occasionally have found a rapid initial exponential rate which they have attributed to increase of blood pressure at the beginning of the test or to movement of the patient. We have found such a component almost always. In our series the only curve that apparently had but a single component was from the left hand of the patient in Case 4, but the clamps were applied before the two components definitely would have been separable. A rapid component was present in the right hand of this same patient. If the test of the left hand had continued for a few minutes after the clamp was released from the pedicle, probably the slower curve would have been apparent. We have checked blood pressures and found that no changes occurred as the test progressed.

Explanation for the two different rates probably lies in the mechanism of clearance of the radioactive material and will be dealt with in another report. A study of the nature of the two components is in progress.

CONCLUSION

A safe, simple, reproducible radioactive isotope test has been successfully applied to a small number of patients in order to determine whether or not the vascularity of skin graft pedicles is adequate. The concept of percentage block has been introduced with the hope that the maximal circulatory block or deficit which is consistent with viability of a graft can be determined.

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A MODIFIED TECHNIQUE OF VEIN STRIPPING

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FOR SEVERAL YEARS a modified method of vein stripping has been under study. The dissatisfaction with existing methods stemmed from the fact that the procedures did not embody good surgical principles. With intraluminar or extraluminar stripping, the same objections were applicable whether the instruments of Mayo, Babcock, or Meyer were used.

Stripping by conventional methods condones the breaking of small venous tributaries and seeking to control any venous ooze postoperatively by pressure with towels, elastoplast, or wrapping with ace bandage. At times, extensive blood loss has occurred in spite of attempted control. Some investigators have stated that when a large tributary was encountered with a stripper, it could be identified and, if necessary, a secondary exploratory incision could be made to facilitate its ligation. However, those who have had experience in stripping know that all veins and tributaries, in spite of their size, do not have the same consistency. Some have firm and strong mesothelium and others are very thin and friable. For this reason, even large tributaries or communicating veins have been broken by the stripper without being previously identified and then ligated.

In addition, it was realized that the postoperative ooze from small broken unligated tributaries was not controlled by the pressure dressings. At times, there were large ecchymoses with local edema, and some produced local hematomas which necessitated evacuation. At times, infected wounds or suppuration along the course of the stripped vein occurred. Increased disability was also noted and, in some, protracted hospitalization with pain in the legs and inability to walk. A further complication was the increase in the incidence of deep phlebitis postoperatively. The proportion of swollen legs complicating surgery seemed too high. For these reasons a modified procedure was sought.

The foregoing observations resulted from my own experience or from comparing results with other surgeons. Some surgeons evaluating stripping do not concur in these observations on complications and seem quite satisfied with the method of stripping generally used. They report a small percentage of patients with postoperative complications, disability, or deep phlebitis. It is unquestionably true that stripping, by whatever method, is preferable to multiple point ligation not only as far as immediate removal of the veins but also in regard to the recurrence and necessary additional injections. However, it is generally conceded that conventional stripping does carry a higher morbidity rate in comparison to the multiple ligation technique. A modification was therefore sought to improve the method and still retain the advantages of stripping. The proposed procedure is simple, direct, and of equal advantage to instrument stripping.

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PROCEDURE

With the patient in the upright position a percussion test to locate the vein is used. The skin is marked by beginning at the groin over the point of impulse, and the vein is then followed downward to the lowest possible point, the skin being marked with indelible solution. This procedure is usually quite simple and allows good portrayal of the course of the vein which is sometimes altered after the patient is reclining on the operating table. As previous study has been made with both the Trendelenburg tests and the tourniquet, the communicating veins are marked as well as the full course of the vein. These are readily found by using two tourniquets and noting the position of the "blow-outs" between the deep and superficial system. The patient is then returned to the operating table, a transverse incision is made in the groin at the highest possible point over the foramen ovale, and the long saphenous vein and its superior tributaries are ligated and transfixed at the junction with the femoral vein. Extraluminar dissection with the finger is then commenced from this point downward (Fig. 1). With the finger it is possible to feel all tributaries as they are encountered. If a circular, rotary motion is made, first on the anterior surface of the vein and then on the posterior surface, dissection can readily be accomplished. When the dissection has been ad-

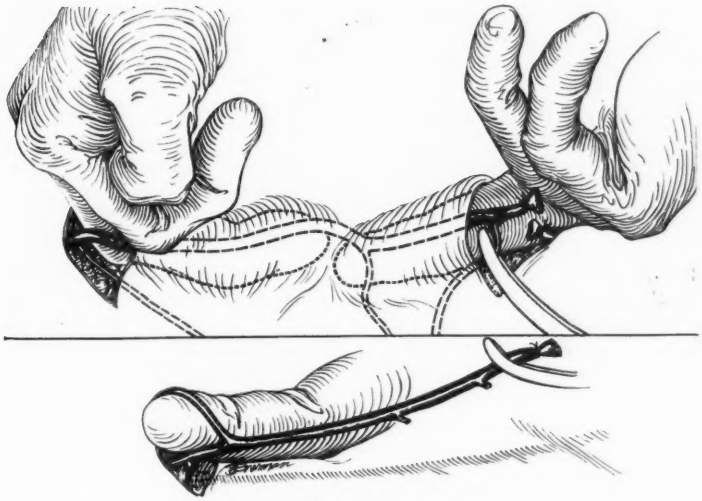

FIG. 1. Technique of operation.

vanced downward with the finger as far as possible, the vein can be tugged slightly, and while the indelible markings and the position of the vein at this level are noted, another incision is made, usually at about the junction of the middle and upper portions of the thigh. The finger is again inserted along the vein and the dissection is continued at this level from below upward. The dissection of the upper saphenous system is thus carried out with the tributaries ligated as they are encountered. The proximal vein is then delivered through the second incision, and the same maneuver is carried out to a lower level. A third incision is usually necessary just above the knee, and a fourth just below it, the distance between incisions being predicated on the probing length of the two index fingers. The technique in the lower leg is the same as that followed in the thigh, finger dissection followed by tributary isolation and ligation.

By this method it can be seen that possibly one or more additional incisions will be necessary as compared with conventional stripping. The average number of incisions is 5 or 6. The lower end is similarly transfixed with chromic No. 3-0 catgut. The incisions are closed with mattress sutures of black silk. Should the short saphenous vein also be involved, the patient can be turned over and the procedure performed on the vein up to the popliteal space.

The patient is out of bed the next day, with no external pressure or support, and usually is home the same day or the next. There are few complaints except for local wound soreness. Inflammatory reactions in the leg, swelling, or any severe disability have very rarely been encountered.

DISCUSSION

The obvious advantage of this method is that there is no doubt as to whether tributaries and communicating veins have been isolated and ligated. By the method of extraluminar or intraluminar stripping, as previously proposed, most of the large tributaries are probably found but certainly not the small veins nor even some of larger caliber. For these reasons, there has been some postoperative bleeding, despite pressure dressings, and more disability in the leg than with the present method. The one disadvantage of this method over conventional methods is that it requires one or two additional incisions. However, when a large tributary is encountered with conventional stripping an additional incision is also necessary.

Thin individuals with enlarged veins offer a problem, as the finger stripping is difficult from the upper third of the lower leg to the point near the ankle. The skin is tight and the subcutaneous tissue is minimal with the fascia overlying the muscles of the lower leg close to the skin. In such instances, it is difficult to insert the finger between the fascia and the skin to complete the dissection.

In discussing the technique of stripping, some workers have mentioned "tunneling" with the finger. The procedure described might be called a continuous tunneling method of stripping as it actually gives a dissection with the finger beneath the skin in the long saphenous vein tunnel. However, to my knowledge this complete technique has not been reported.

Early in 1955, serious study of this method was begun, at first with a modified technique and partial finger dissection in conjunction with stripper. In the past 5 years, 376 operations have been performed with finger dissection alone. Analysis of these cases reveals that the complications have been minimal. There has been no mortality and only minimal morbidity. Sixty-eight patients have complained of swelling of the lower leg following the procedure for a period of 3 weeks or less. Only 3 have complained of persistent swelling signifying a complicating deep phlebitis. In 1 a pulmonary embolus occurred on the tenth day postoperatively. There was local wound reaction in 2. In 302, local reaction or complaints were minimal.

Very few injections have been necessary postoperatively, and although the period of study covers only 5 years, it is thought that recurrences will be no more than previously reported. This technique should provide as good results as conventional methods of stripping regarding both recurrences and necessary injections after stripping.

SUMMARY AND CONCLUSIONS

A method of stripping of the long or short saphenous vein for varicose veins is suggested. This method is an extraluminar dissection of the vein with the finger through multiple incisions by using the finger above and below to dissect the vein and locate its tributaries. All tributaries are ligated, even to the smallest, as they are encountered. No pressure dressings are used postoperatively; only small dressings are used to cover the multiple incisions.

It is believed that the complications and morbidity resulting from this method of stripping are less than from conventional methods. It appears to be a better surgical procedure to ligate tributaries by direct vision with a ligature rather than to depend on pressure dressings along the course of the dissection to obtain hemostasis. There is less blood loss than with conventional methods of stripping, and complications are minimal. Convalescence is shortened and more comfortable, with less hospitalization necessary. The procedure provides results equal to previous stripping techniques as to recurrence and necessary subsequent injections.

MANAGEMENT OF UNSTABLE TROCHANTERIC FRACTURES

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MOST TROCHANTERIC FRACTURES are now treated by open reduction and internal fixation. The advantages of this method have become obvious as the result of experience, as reported by Cleveland and associates (3), Evans, and others. Morbidity from the fracture is greatly decreased, and the patient can generally be allowed out of bed in a wheel chair the day after surgery. Nursing care is facilitated, and the period of hospitalization is materially shortened. Our private patients usually are discharged home in 2 weeks, unless there is some unusual complication. Most important, the mortality rate has been markedly reduced as compared with that among patients treated by traction or in body casts; in many hospitals this reduction has been over 50 per cent. Cleveland (2) reported that the incidence of senile psychosis was approximately 5 times less among patients treated by operation as compared with those treated by nonoperative methods.

Trochanteric fractures have been classified in various ways. For convenience, one will be followed that has been described previously (1) which divides the fractures into four groups (Fig. 1). Type 1 is a linear fracture through the trochanteric region, type 2 is a comminuted fracture through this region, type 3 is a trochanteric fracture with an associated subtrochanteric element, and type 4 is an oblique fracture of the upper portion of the shaft of the femur involving the subtrochanteric region. The last type may or may not be associated with a type 1 or a type 2 fracture. Types 3 and 4 usually require fixation in addition to a nail-plate to insure stability.

The chief complication in the type 3 fracture is medial migration of the distal fragment as a result of the pull of the adductor muscles. As a result, the nail may push its way through the articular cartilage of the head of the femur and into the acetabulum (Fig. 2). Various methods will be described to prevent this complication.

Not all trochanteric fractures with a subtrochanteric element, type 3, necessarily require additional internal fixation other than the nail-plate; they may be self-locking after reduction (Fig. 3). Here the fracture line appears in the shape of a church steeple. Ideally the nail should be placed in the superior portion of the neck in these cases, because a low insertion may sheer off

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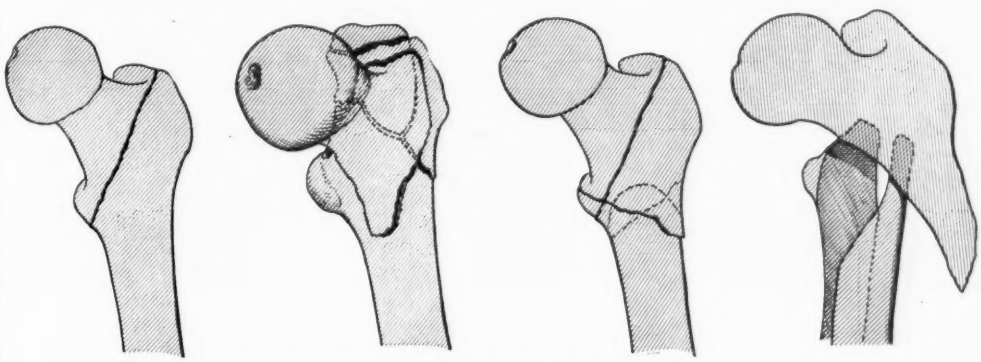

TYPE 1. TYPE 2. TYPE 3. TYPE 4.

FIG. 1. Four types of trochanteric fractures.

FIG. 2.

FIG. 3.

FIG. 2. A type 3 fracture showing medial migration of the distal fragment with protrusion of the nail into the pelvis. This could probably have been prevented by the use of a buttress plate.

FIG. 3. A type 3 fracture which is of the self-locking "church steeple" type does not require additional fixation.

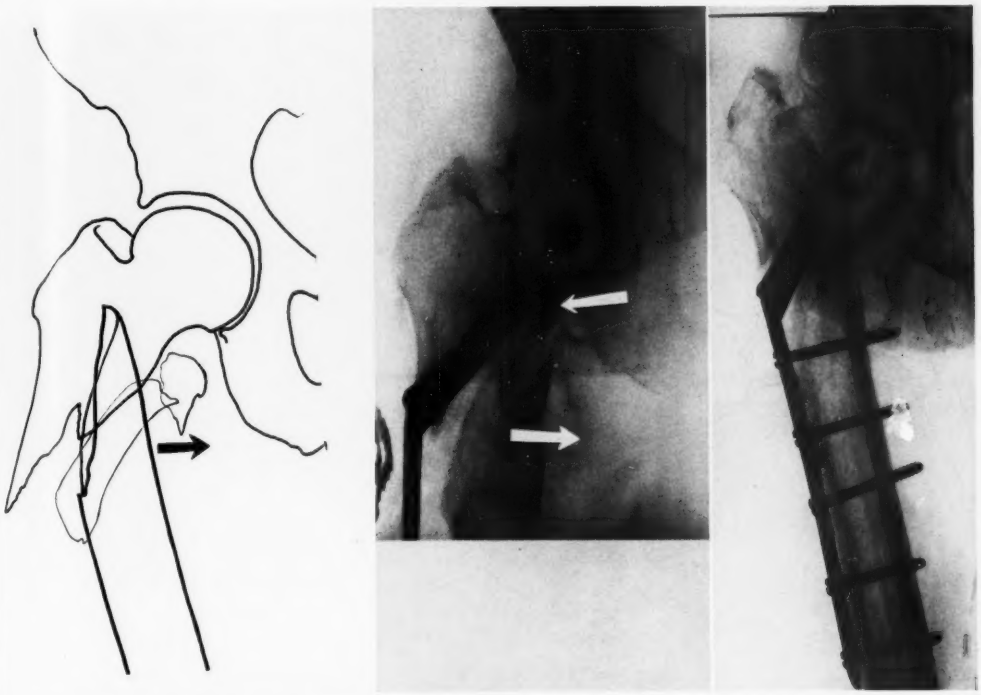

FIG. 4. In this type 3 fracture, medial migration has been prevented by placing the nail parallel to and in contact with the inferior and medial cortex of the femoral neck.

the "steeple." Medial migration in this type of fracture is prevented by the impingement of the medial aspect of the steeple against the medial cortex of the proximal fragment.

Medial migration can sometimes be prevented by placing the nail parallel to and in contact with the inferior and medial cortex of the neck of the femur (Fig. 4) so that the tendency of the distal fragment to shift medially is counteracted by the abutment of the nail against the cortex. This is the simplest and probably the best method of preventing medial migration in type 3 fractures, except in the self-locking church-steeple variety described. However, it is not always mechanically possible to place the nail in this position. Also, in some cases, the medial cortex of the neck may be too comminuted to support the nail (Fig. 5). Here, the nail was placed in apposition to the medial cortex of the neck and in a valgus position. The nail was not too long. Nevertheless, medial migration occurred, and the nail penetrated through the hip joint into the ilium. Additional internal fixation should have been used; medial migration could have been prevented in this case, probably, by use of an auxiliary buttress plate (Fig. 6). The decision to use a buttress plate is often made at the time of operation, as the nail may have been placed in the center of the neck when ideally it should have been in contact with the medial cortex. In this event it is preferable to use an auxiliary plate rather than to withdraw and reinsert the nail, because after a second insertion the nail is never so secure. Also, an auxiliary plate is indicated when a type 1 or type 2 fracture is converted at operation to a type 3 fracture.

Two types of buttress plate have been used. One is an ordinary four-hole plate in which the top screw in the nail-plate is placed through the second hole from the bottom of the buttress plate. One or two screws may be placed through the upper holes of the buttress plate into the trochanter and neck; these are not necessary for fixation of the fracture but prevent rotation of the plate. The second type of buttress plate is preferred, which is especially made to match the

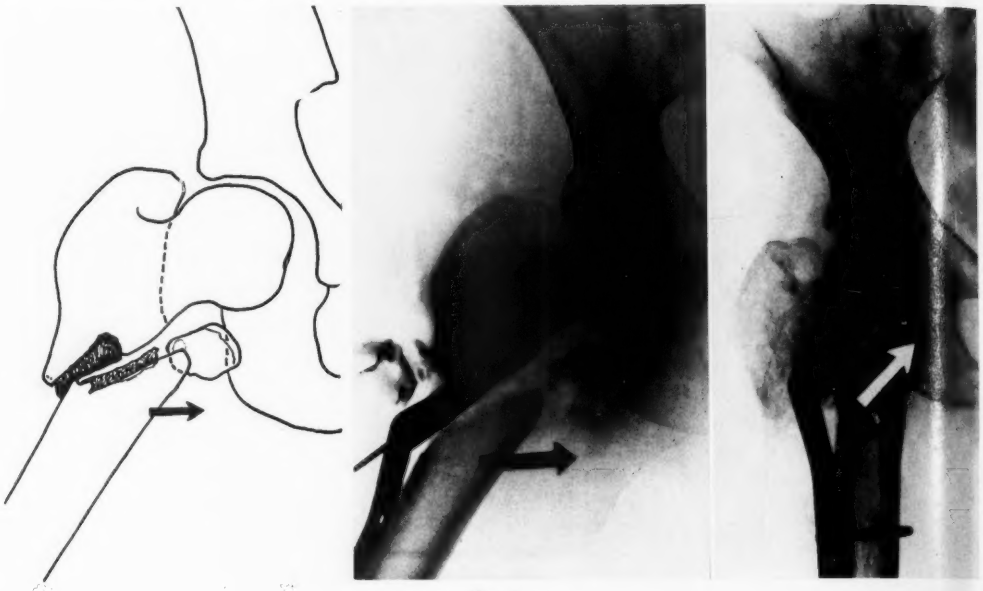

FIG. 5.

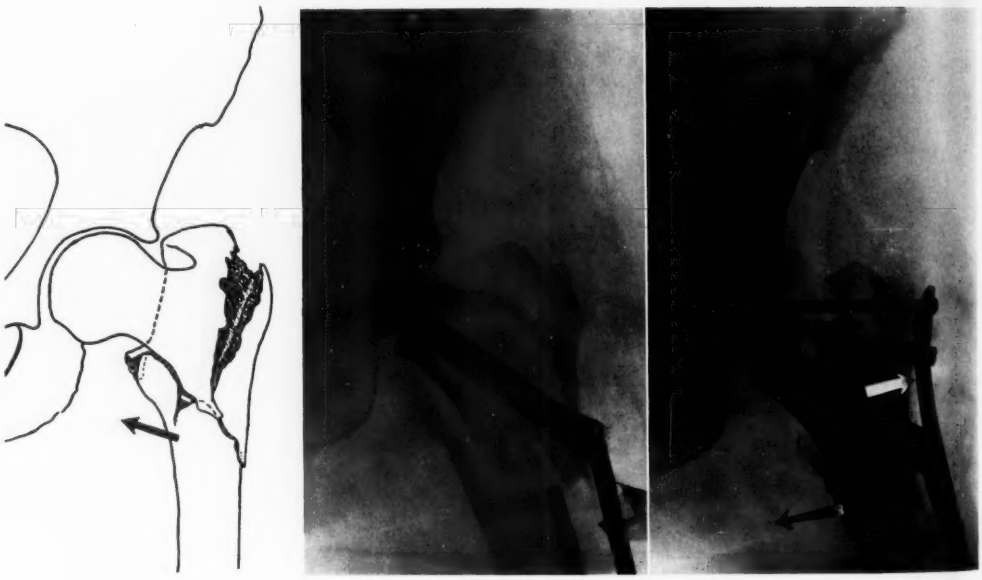

FIG. 6.

FIG. 5. In this type 3 fracture, the nail was placed in apposition to the medial cortex of the neck and in a valgus position; nevertheless, it penetrated the hip joint because the medial cortex of the neck was too comminuted to prevent migration. Additional internal fixation should have been used.

FIG. 6. An unstable type 3 fracture stabilized by a buttress plate.

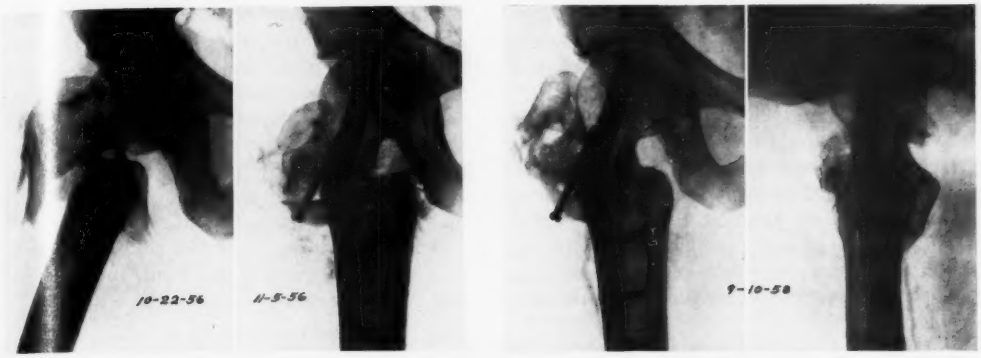

FIG. 7.

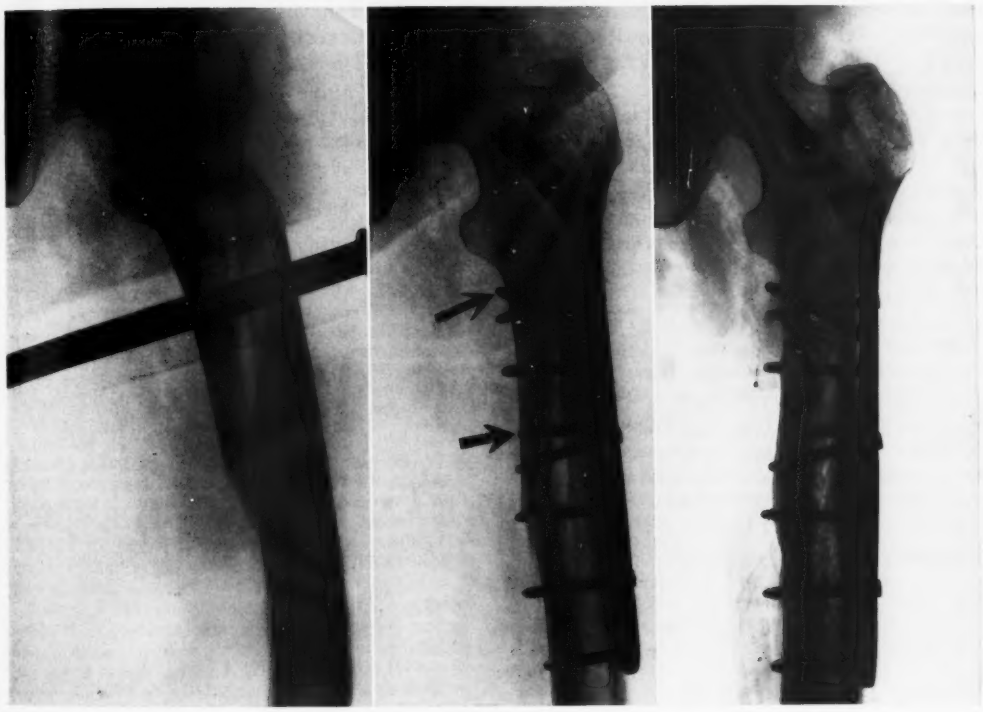

FIG. 8.

FIG. 7. Intentional medial displacement of the distal fragment to stabilize a comminuted subtrochanteric fracture.

FIG. 8. A type 4 fracture with two-plane fixation. Arrows point to screws placed at approximately a right angle to the nail-plate.

upper portion of the nail-plate so that the upper two screws in the nail-plate pass through the buttress plate.

In markedly comminuted subtrochanteric fractures in which the comminution also involves the greater trochanter, the trochanteric region is too shattered to support a buttress plate. Under these circumstances, it is best to anticipate medial migration by displacing the distal fragment medially two-thirds of the diam-

eter of the bone. This enables the medial cortex of the neck to impinge on the lateral cortex of the distal fragment. The comminuted portion of the trochanter is retracted and the nail is inserted under direct vision into the cancellous bone of the proximal fragment. It is preferable if the hip is in a valgus position. The comminuted portion of the greater trochanter is then replaced over the nail-plate junction. The end result in these patients resembles that of a subtrochanteric osteotomy, a principle which has been used for a number of disorders of the hip. Figure 7 demonstrates this method.

In type 4 fractures, the oblique fracture in the upper portion of the shaft is reduced and held in position by two or more screws placed at an angle as nearly 90 degrees as possible to the anticipated plane of the screws which will secure the nail-plate. Occasionally it is preferable to use wire loops circumferentially, placed with a Stille wire carrier, about the shaft of the femur. After this preliminary step, a nail-plate is inserted in the usual way. The length of the plate will depend upon the location and extent of the fracture but should be long enough to allow at least two or three screws below the distal end of the oblique fracture (Fig. 8).

In order to ascertain how often additional internal fixation is needed, 100 consecutive trochanteric fractures have been reviewed. There were 63 uncomplicated types 1 and 2 fractures. Eight type 1 or type 2 fractures were converted to type 3 fractures at operation, i.e., a subtrochanteric element was produced by insertion of the nail. The total number of type 3 and type 4 fractures, 20 and 9 respectively, including those converted, was 37. The kinds of fixation used in treating these 37 were as follows: an auxiliary buttress plate was used in 11, additional screws in 5, and wire loops in 5; the Jewett nail-plate alone was used in 16. Upon reviewing the postoperative roentgenograms of these 16, and the clinical results, it is clear in retrospect that 5 of the 16 should have had additional internal fixation. In 11 of the 37, the nail-plate alone was sufficient.

Before reviewing this series of 100 fractures, we did not suspect that additional internal fixation would be indicated in 26 per cent.

SUMMARY

1. In unstable trochanteric fractures, medial migration of the distal fragment with protrusion of the proximal end of the nail into the hip joint and pelvis is a complication more frequent than is generally appreciated.

2. Several methods of preventing this complication are described, including additional fixation with a buttress plate.

3. In a series of 100 consecutive trochanteric fractures, it was found that additional internal fixation was or should have been used in 26.

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EXTERNAL PANCREATIC FISTULA

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AN EXTERNAL PANCREATIC FISTULA is so rare a complication that few surgeons have the opportunity of gaining any wide experience in its treatment. Reports on the subject are usually based upon single cases together with others collected from the literature. In this report I present the cases of 3 personally treated patients with pancreatic fistula, 2 managed with current methods and 1 operated upon by a technique not used earlier for that disorder.

CASE 1. A 65 year old male had a Billroth II partial gastrectomy for duodenal ulcer. Acute pancreatitis with diastasuria developed on the second postoperative day, and on the third day the serum bilirubin values rose. When the bilirubinemia still showed a tendency to rise, laparotomy was again performed on the fourteenth day after the initial operation. Plentiful fat necrosis was present in the abdominal cavity. The pancreas was greatly swollen. Below the liver, toward the foramen of Winslow, a more than fist-sized abscess was found containing a white, turbid fluid. Culture of samples of this fluid showed no growth of pathogenic bacteria. A cholecystojejunostomy was performed. Using continuous suction the abscess was drained of as much as one-half liter per 24 hours of white, turbid fluid with high diastase activity. After a new episode of pancreatitis, the fluid in the drain became bile-stained. Figure 1 shows the irregular fistulous tract in communication with both the horizontal duodenum and the transverse colon. The biliary tract and pancreatic duct were not visualized on the roentgenogram. After a further 3 weeks treatment with atropine and continuous suction, the fistulous system closed. Since, it has not reopened, and the patient has been free from symptoms during the 6 months which have elapsed.

CASE 2. A 53 year old male, whose history suggested common duct stone and acute pancreatitis underwent operation during a remission. A pancreatic cyst was found below the liver which extended far below the stomach, the gallbladder being incorporated in its wall. Cholecystectomy was performed. Peroperative cholangiography revealed normal deep bile passages. The cyst was drained and treated with continuous suction for 2½ months and subsequently drained without suction for approximately 6 months. Throughout this period, pancreatic secretion without the admixture of bile escaped through the fistula. Figure 2 shows the fistula to enter a cavity measuring just over 5 centimeters in diameter from which the main pancreatic duct was filled with contrast medium. The biliary tract was not visualized. The patient underwent reoperation. The fistulous tract was mobilized and fistulogastrostomy performed. The patient has since been free from symptoms for more than 15 months.

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CASE 3. A 58 year old male had had a Billroth II partial gastrectomy 4 years earlier for duodenal ulcer. Acute pancreatitis, wound rupture, and pancreatic fistula supervened during the postoperative period. The fistula closed spontaneously but subsequently reopened 2 or 3 times a year in connection with exacerbations and formation of abscess. During remissions, the patient suffered from a dull aching and a feeling of tension in the epigastrium. Cholecystography indicated gallbladder disease was present; cholecystectomy was performed 18 months after the partial gastrectomy. Peroperative cholangiography showed the biliary tract to be normal. However, the epigastric symptoms persisted unchanged and signs of pancreatic insufficiency with steatorrhea appeared and there was loss of weight. The patient was greatly depressed by the constant pain.

Figure 3a and b revealed a fistulous tract in communication with a distended main pancreatic duct. No contrast medium passed over into the intestine. At reoperation, approximately 4 centimeters of the pancreatic tail were resected. The pancreatic duct at the site of resection was some 3 millimeters in diameter; about 4 millimeters of the duct were left projecting outside the amputated pancreatic surface. This portion of the duct was cut open into 2 flaps which were reflected and fixed to the pancreatic surface with interrupted silk sutures. A steady flow of pancreatic juice escaped through the duct. The whole amputation surface of the pancreas was then anastomosed to the proximal jejunal segment in the form of a Roux en-Y arm. The mucosa in the jejunal loop was sutured to the pancreatic capsule. The serosa was invaginated over this row of sutures and fixed in turn to the pancreatic capsule with interrupted silk sutures (Fig. 4). The postoperative period was uneventful. The pancreatic fistula closed in 5 days and has not since reopened. The patient gained 7 kilograms in weight during the first 3 months. He is now free from discomfort for the first time in 4 years.

DISCUSSION

The usual cause formerly underlying the formation of a pancreatic fistula was marsupialization of pancreatic cysts. Nowadays the fistula is more often the result of damage to the pancreas at gastric resection, biliary tract operations, or splenectomy. Of the cases which I have reported, 2 were subsequent to partial gastrectomy (Cases 1 and 3) and 1 followed drainage of a pancreatic cyst (Case 2).

FIG. 1.

FIG. 1. Case 1. Roentgenogram reveals an irregular fistulous tract in communication with the horizontal duodenum and the transverse colon. Neither the biliary tract nor the pancreatic ducts are visualized.

FIG. 2.

FIG. 2. Case 2. Roentgenogram shows the fistula to communicate with a cavity in the region of the pancreatic head, from which Wirsung's duct is filled with contrast medium.

Most external pancreatic fistulas close spontaneously. In a series of 33 cases of pancreatic cysts treated by drainage, no fistula remained open for more than 2 years and most of them closed within 12 months. The course is often surprising. Even fistulas from which the outflow has for several months been large may close spontaneously. However, it not infrequently happens that, as in Case 3 described herein, the patient suffers constant epigastric pain when the fistula has closed, and that it reopens from time to time. Even if the pancreatic fistula is the direct result of a surgical procedure, and the pancreas is initially healthy, it may be damaged by progressive fibrosis. The portion of the pancreatic tail resected in Case 3 showed features of chronic fibrosing pancreatitis with atrophy of the exocrine pancreas.

Treatment of a pancreatic fistula is in the first place conservative. The skin around the fistulous orifice should be protected against digestion. Effective drainage of the fistulous tract protects the skin and aids closure. The local application of aluminium compounds, tannic acid powder, and 1 per cent acetic acid and other preparations has been proposed. Silon® ointment together with drainage afforded adequate protection in the cases herein reported.

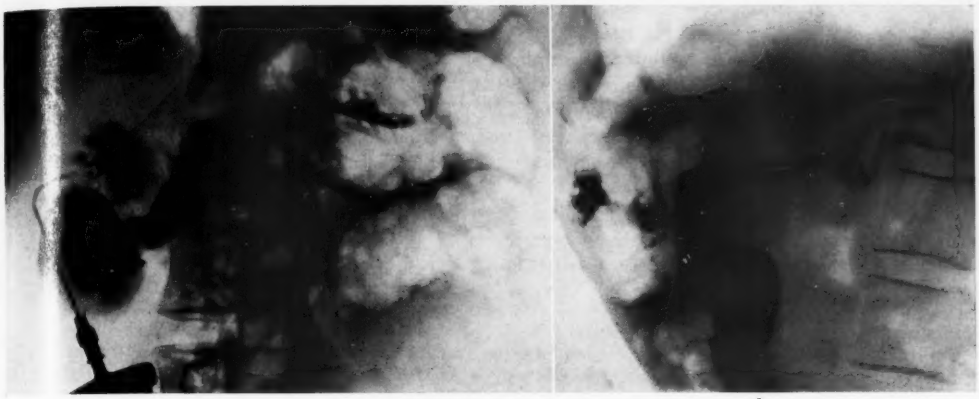
Dietary measures and different drugs such as ephedrine, atropine, banthine, and probanthine have been given to reduce the external pancreatic secretion. However, the value of these forms of treatment has been questioned.

If a pancreatic fistula fails to close after 6 to 12 months of conservative therapy, operation is indicated. In timing the operation, consideration must be given to the patient's symptoms, electrolyte losses, digestion of the skin, and the like. The gravity of a pancreatic fistula has been demonstrated experimentally. A total fistula of this type leads to death in the dog within 5 to 8 days.

In this connection it may be noted that in order to prevent the formation of an external fistula, Lahey and Lium in 1937 recommended initial drainage of pancreatic cysts to the proximal portion of the alimentary tract instead of marsupialization. They referred to a collected series of 9 patients treated successfully with this technique.

Several methods have been proposed for the treatment of pancreatic fistula, such as section of the sphincter of Oddi, transplantation of the fistula with anastomosis to the proximal segment of the alimentary tract, and excision of the fistula down to the pancreatic duct with mucosa-to-mucosa anastomosis of the duct to the duodenum or jejunum.

For clinical purposes the simplest method is to transplant the pancreatic fistula, but these transplanted fistulas frequently stenose. If the obstruction in the pancreatic duct is situated proximally, pain recurs. If the fistula issues from the tail or body of the pancreas, resection of the pancreas together with the fistulous tract is the method of choice. If the fistula issues from the



a b

FIG. 3.

FIG. 3. Case 3. a, Roentgenogram reveals a fistulous tract in the midline, extending dorsally, and b, in communication with a dilated duct of Wirsung.

FIG. 4. Case 3. A swallow of contrast medium shows a jejunal loop resembling a Roux en-Y anastomosis drawn up high under the left diaphragmatic arch.

terminal portion of the pancreatic duct, transplantation should initially be given a trial.

In Cases 2 and 3, in which the pancreatic fistula did not close spontaneously, the fistula issued from the pancreatic duct in the head of the organ. In Case 2, the fistula was transplanted to the stomach, and the results have been favorable during the 15 months which have elapsed since the operation. The frequent exacerbations accompanying recurrences of the fistula in Case 3 suggested surgical treatment directed to the region of the fistula itself to be unsuitable. When roentgenography of the fistulous tract showed the pancreatic duct to be greatly dilated—suggesting a terminal obstruction—an operation permitting retrograde drainage of the pancreatic duct appeared to be indicated. Retrograde drainage of the pancreatic duct was used by Puestow in the treatment of chronic pancreatitis. In the author's case, the anastomosis of the amputated pancreatic surface to the jejunal loop was made by a method resembling the procedure in Whipple's operation. The result is promising. As only 6 months have elapsed since the operation, no more final opinion is justified.

FIG. 4.

CONCLUSION

The first procedure to be given a trial in the operative treatment of a fistula issuing from the terminal segment of the duct of Wirsung should be transplantation of the fistula to the proximal portion of the alimentary tract. If this measure fails, or if local conditions suggest it to be unsuitable, retrograde drainage of the pancreatic duct system may be indicated. If roentgenography shows the main pancreatic duct to be fully patent proximal to an obstruction situated in the head of the pancreas, anastomosis between the whole amputation surface of the pancreatic tail

and the proximal jejunal segment in the form of a Roux en-Y arm secures adequate retrograde drainage. The procedure is technically simpler than the mucosa-to-mucosa anastomosis between the pancreatic duct and the duodenum or jejunum as proposed by Cattell and Warren.

SUMMARY

Three cases of pancreatic fistula are reported, 1 of which was managed conservatively and 2 operatively. One of the latter patients was treated by an operative technique not used earlier in such cases.

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THE SURGEON'S LIBRARY

Reviews of New Books

THE *Atlas of Clinical Hematology*[1] is a compendium of colored plates from a collection of camera lucida drawings which have been prepared by the author during a 25 year period. The colors are an accurate representation of a modified Romanowsky stain, and the cells are depicted at a magnification of about 1,000. Each plate is preceded by a brief introductory description of the hematologic normal or disease state it illustrates. A suitably labelled line drawing and a short legend accompany each plate for purposes of cell identification. Selected references are included with each illustrated topic.

Subscribing to the monophyletic school of hematopoiesis, the author begins the volume with an illustrated schematic drawing of this unitarian theme. This sets the stage for the nomenclature to be subsequently utilized and permits a depiction of normal cell types. Next, 5 plates and the attendant text describe the normal picture in the peripheral blood and bone marrow of the fetus, infants, and children. Thereafter, the text and illustrations cover pathologic hematology in infancy and in adult life.

The drawings are excellent in that they are basically clear representations of cell types. For comparative laboratory purposes they represent a good instructive aid. As in most camera lucida reproductions there is a loss of the subtle nuances of color and texture which may be appreciated by direct microscopy or which may be more fully appreciated in a well made color photomicrograph.

Pathologic states are generally well covered. However, notable exceptions are present. Thus, the bizarre cell types seen in some macroglobulinemic syndromes are not illustrated. Absent, also, are representations of red cell morphology in disorders such as sickle cell trait, myelofibrosis, and acanthocytosis.

Errors in the text matter are minimal. Discrepancies between the labeling of the line drawings and the plates are very rare, as in Plate 70 in which a basophilic stab cell is labelled as neutrophilic. Morphologists might question an occasional cell identification, for example, free nucleus of a normoblast versus small lymphocyte—Plate 5; plasmacyte versus abnormal lymphocyte in several plates. However, the final arbiter could only be direct microscopy, if indeed that could settle some of the age old morphologic arguments.

[1]ATLAS OF CLINICAL HEMATOLOGY. By Katsuji Kato, Ph.D., M.D. 296 pages, 92 colored illustrations. $25.00. New York and London: Grune & Stratton, 1960.

The references are adequate for the purpose of the book. However, one wonders at the relative infrequency of more recent references to electron microscopy which have tended to help resolve morphologic differences. They are more useful than the older references from the literature which are inclined to carry one backward into the quagmire of morphologic controversy.

The index is sufficiently cross-referenced. The quality of the color reproductions is good. This volume will find its place as one of the better atlases of hematology and is to be recommended to those with a particular role in the teaching of morphologic hematology. —*Walter Rambach.*

THE HARD COVER BOOK entitled *The Management of Fractures and Soft Tissue Injuries*[2] is a combination of the seventh edition of *An Outline of the Treatment of Fractures* and the second edition of *Early Care of Acute Soft Tissue Injuries*, both of which are published separately in paper back form. The first 137 pages are devoted to fractures and cover the general principles and pathophysiology, immediate first-aid care, and definitive care including instructions in the taking of roentgenograms of various fractures. This is followed by a discussion of the treatment of individual fractures, from the skull to the phalanges of the feet. Common fractures of childhood are dealt with separately as are matters of anesthesia. A detailed chapter on operative management is followed by one on care of multiple injuries. Rehabilitation and measuring of joint function are accorded separate chapters. At the bottom of each of the first 26 pages, in bold type, is one of the fracture aphorisms and these are repeated on the final pages of the fracture section as a suitable summation. Soft tissue wounds, pages 141 through 359, are discussed in general, covering primary assessmen[t] of the patient, infection, anesthesia, shock, and burns. Then the wounds by region and organ system are presented with points in diagnosis, criteria for operative procedures, postoperative care, and late management. A final chapter deals with bites.

The book is concise but clear, detailed but discriminating, authoritative but orthodox. The basic material is in good balance with the more practical

[2]THE MANAGEMENT OF FRACTURES AND SOFT TISSUE INJURIES. By the Committee on Trauma, American College of Surgeons. Based on An Outline of the Treatment of Fractures, 7th ed., and Early Care of Acute Soft Tissue Injuries, 2nd ed. 372 pages, illustrated. $5.00. Philadelphia and London: W. B. Saunders Co., 1960.

"how-to-do-it" material. Although a wealth of information is presented, even the combined volume is coat-pocket size. The text is easily read and the index adequate. —*Warner F. Bowers.*

ANY VOLUME which deals almost entirely with the normal structure, and as technical as a monograph on roentgenologic diagnosis must be, is apt to be difficult to read. This is not so, however, with the book entitled *The Normal Skull; a Roentgen Study.*[3] The type setting and the illustrations are so exceedingly clear that reading is facilitated. In general, the discussion of the roentgenographic appearance of the skull is preceded by brief yet very clear anatomic descriptions of the part, or parts, in question. The anatomic descriptions of the various bones comprising the skull are exceedingly good and the illustrations are beautifully done.

Although this is not a long monograph in comparison with others, it contains some excellent detail which is best exemplified in the chapter on the foramina of the normal skull. Another example of the careful attention which has been given to detail is in the illustration of air trapped in the conjunctival sacs, a finding which would escape all but the most astute observer. There are many small bits of information in the monograph which would be of value to the neurosurgeon.

Illustrations of pathologic conditions are sufficient to emphasize the normal variations in structure. These are limited in number but are useful in demonstrating the normal variations in the sella turcica.

A few of the statements made can be considered to be controversial. Thus, the authors state that, in their opinion, less than 50 per cent of the acoustic nerve tumors show unequivocal changes in the roentgenogram. This is at considerable variance with the experiences which have been gained elsewhere, particularly in Scandinavia. —*John E. Adams.*

WHEN THE FIRST EDITION of *Treatment of Cancer and Allied Diseases* was published in 1940, there were 3 volumes which encompassed most of the essential knowledge in this large field. During the past 20 years, progress in the treatment of neoplastic diseases has been so rapid that the second edition of this ambitious undertaking by Pack and Ariel has been expanded to 9 volumes.

Volume IV, which is the subject of this review, is confined to *Tumors of the Breast, Chest, and Esophagus.*[4] Sixty-seven authors have contributed and, almost without exception, they are widely known and generally recognized as authorities in the subjects which they have discussed.

In this book, the objectives of the entire series of 9 volumes have been kept clearly in mind. "The care of the patient is emphasized throughout, and palliative procedures are presented with the same emphasis given to measures aimed at cure." Moreover, I am impressed with the wise judgment of the editors in selecting authors who have very ably presented subjects which, at this moment, are highly controversial, such as radical mastectomy versus simple mastectomy combined with x-ray therapy, and radical pneumonectomy versus standard pneumonectomy. The sections on x-ray therapy and other palliative measures which are useful in the treatment of tumors of the breast, lungs, and esophagus, should be especially helpful for surgeons who do not ordinarily find these aspects of management adequately covered in a book which describes the surgical therapy in detail. Recent developments in bringing various portions of the gastrointestinal tract up into the thorax or neck, to replace or to bypass the esophagus, are clearly described, with suitable consideration for the limitations and complications of these procedures.

Nearly every chapter is well organized and clearly written. For the most part, the photographs, charts, and drawings are excellent. This book should be of value for students as well as for those engaged in specialized fields of treatment, particularly because of the historical orientation and the completeness as regards all facets of these subjects. —*Charles Kirby.*

IT IS INDEED A PLEASURE to note the appearance of the volume by Stanbury, Wyngaarden, and Fredrickson[5] which covers most of the biochemical defects of a hereditary nature. It represents the collaborative effort of some 46 authors and 3 editors, and will remain for many years to come the most complete and comprehensive review of this rapidly expanding subject. Sir Archibald Garrod will indeed be astounded by the fruits of the Croonian Lectures some half a century later.

The Metabolic Basis of Inherited Disease[5] is particularly strong in the biochemical approach to each of these conditions. Most of the sections are introduced with a summary of the pertinent information in that area before the clinical syndrome is introduced. The biochemical lesion of each disorder is described in considerable detail, and many of the major published charts and diagrams are reproduced in full. The references are extremely complete and were brought up to date within 6 months of publication. The latter represents one of the most valuable assets of the book. Although most of the chapters are good, the sections on the lipidoses by Donald Fredrickson, phenylketonuria by Eugene Knox, and vitamin D-resistant rickets by Franklin Williams and associates are among the most lucid and comprehensive ever written.

The book is weak in a number of areas. For instance, there is no mention of cystic fibrosis of the pancreas, which is certainly one of the most frequently seen and intensively studied genetic entities. Throughout the book, there is insufficient emphasis placed upon the contributions made by genetics toward the

[3]THE NORMAL SKULL; A ROENTGEN STUDY. By Robert Shapiro, M.D., and Arnold H. Janzen, M.D. 257 pages, 645 illustrations. $18.00. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Bros., 1960.

[4]TREATMENT OF CANCER AND ALLIED DISEASES. 2nd ed. Vol. IV—TUMORS OF THE BREAST, CHEST, AND ESOPHAGUS. By 67 authors. Edited by George T. Pack, M.D., F.A.C.S., and Irving M. Ariel, M.D., F.A.C.S. 667 pages, 650 illustrations. $30.00. New York: Paul B. Hoeber, Inc., Medical Division of Harper & Bros., 1960.

[5]THE METABOLIC BASIS OF INHERITED DISEASE. Edited by John B. Stanbury, M.D., James B. Wyngaarden, M.D., and Donald S. Fredrickson, M.D. 1477 pages, illustrated. $30.00. New York, Toronto, London: McGraw-Hill Book Co., Inc., The Blakiston Division, 1960.

development of this rapidly growing field. Finally, the introductory chapter is weak and sketchy and inadequate for the unsophisticated reader.

This book is definitely written for the expert, and as such it should be read by every research worker in biochemical genetics in man. —*David Yi-Yung Hsia.*

THE ATTRACTIVE NEW VOLUME entitled *Complications in Surgery and Their Management*[6] is, in fact, a magnificent new textbook of surgery, especially oriented toward the operative and postoperative periods. It is a far cry from some of the earlier works on postoperative complications which were merely manuals or compendiums, their small size and perfunctory coverage indicating the minor role assigned to such complications in years gone by. The authors, Artz and Hardy, are the editors of a text to which there are 71 contributors. These editors have themselves contributed 3 chapters each, while the remaining 51 chapters have been prepared by men who are outstanding in their respective fields. As the editors point out, a practical discussion of postoperative complications must be written by men of vast experience in order that the fruits of this experience may be passed on to others. Obviously, today no one surgeon can have had such an experience in more than the limited field of his own specialization.

The composition of the volume is of interest. The first half covers, in conventional and traditional fashion, general complications such as infections, problems pertaining to surgical wounds, and those complications occurring in the several systems, e.g., bronchopulmonary, cardiovascular, urologic, and gastrointestinal.

The second part is concerned with the complications of operative procedures in various anatomic areas, e.g., the biliary tract, the spleen, the pancreas, the large and small intestine, the appendix, and also in the more highly specialized fields. It is in this second section, in particular, that the imposing list of authors and the subject matter capture the attention of the reader, when such authorities as Frank Glenn, Robert Zollinger, John Waugh, and many others of equal reputation express their opinions in their own special field of endeavor. Moreover, the material is not restricted to the treatment of complications per se for, throughout, prevention is constantly stressed which involves considerable discussion concerning surgical judgment, indications and contraindications for operation, and the choice of operative procedures to be used.

It is impossible to do justice to all of the material presented in such a brief review as this.

This volume should be popular with members of the resident staff as well as with the more sophisticated surgeons. For the surgeon with limited experience, the anticipation of postoperative complications should be an aid in early recognition and successful treatment and, therefore, this in turn should redound to the welfare of the patients under his care.

—*Henry K. Ransom.*

[6]COMPLICATIONS IN SURGERY AND THEIR MANAGEMENT. Edited by Curtis P. Artz, M.D., F.A.C.S., and James D. Hardy, M.D., F.A.C.S. 1075 pages, illustrated. $23.00. Philadelphia and London: W. B. Saunders Co., 1960.

THERE NEEDS TO BE some justification for publishing a new book in a limited specialty field in which an excellent text already exists. In the case of *Cardiac Disease in Pregnancy*,[7] this requirement is amply met by the vast experience of the Obstetric-Cardiac Clinic of the New York Lying-In Hospital and its Director, Curtis Mendelson. In the past 28 years, 3,690 pregnant patients with complications of organic heart disease of almost all types were cared for in this institution.

Most of these patients have been followed up personally by the author, and in many ways this is a "personal" book. References are numerous but, in general, they are used to expand a series of cases or to report the rarer entities. Basic diagnosis and, especially, treatment reflect very strongly the author's experience and beliefs with the cardiac patient during pregnancy.

Of 16 chapters, the first 2 concern physiology and the general problems of cardiac disease in pregnancy, while the remaining 14 are each devoted to some particular type of heart disease as influenced by pregnancy. There are numerous tables and diagrams and a few illustrations. Occasional typographic errors are noted and some of the diagrams, particularly those borrowed from other sources, tend to be inadequately labeled or described. These minor points are counterbalanced by the author's personal expressions of opinion and occasional welcome touches of humor. This is an excellent reference book and anyone confronted with a pregnant cardiac patient, no matter how obscure the problem, can surely find guidance in its pages. —*Warren H. Pearse.*

THE WELL WRITTEN BOOK *Resuscitation of the Newborn Infant*[8] is edited by Harold Abramson, Professor of Pediatrics of New York Medical College. It is a collaborative effort of specialists in the related clinical and laboratory fields. All of these contributors are members of the Special Committee on Infant Mortality of the Medical Society of the County of New York.

In the first chapters physiology, biochemistry, and pathology of the newborn infant are reviewed. These are well documented with current research references. The following chapters, particularly, should be of vital interest to the obstetrician: "Diagnosis of Fetal Distress," "The First Sixty Seconds of Life" and "Resuscitation Procedures in the Delivery Room." The section on mechanical respirators and resuscitators includes a comprehensive table of the characteristics of 21 machines commonly in use, and the author concludes that a "manually operated control is probably more expedient to use than an automatic commercially available cycling machine."

A recovery room for high risk newborn infants is recommended for which a floor plan with list of equipment is presented as well as suggested nursing policies. Obstetricians, pediatricians, and those in residency training could benefit from reading the

[7]CARDIAC DISEASE IN PREGNANCY. By Curtis L. Mendelson, M.D. 371 pages, 141 illustrations. $13.50. Philadelphia: F. A. Davis Co., 1960.

[8]RESUSCITATION OF THE NEWBORN INFANT. Edited by Harold Abramson, M.D. 245 pages, 36 illustrations. $10.00. St. Louis: The C. V. Mosby Co., 1960.

chapters on examination of the newborn infant as well as the very excellent and practical section on laboratory diagnosis. Extensive references are listed at the end of each chapter.

The authors are to be congratulated on a well unified presentation that is both scholarly and practical. The format and typographic design afford easy reading. —*Charlotte Herman Kerr.*

BOOKS RECEIVED

Books received are acknowledged in this department, and such acknowledgement must be regarded as a sufficient return for the courtesy of the sender. Selections will be made for review in the interests of our readers and as space permits.

Pharmacology; the Nature, Action, and Use of Drugs. By Harry Beckman, M.D. 2nd ed. 748 pages, 105 illustrations. $15.50. Philadelphia and London: W. B. Saunders Co., 1961.

The Hand; a Manual and Atlas for the General Surgeon. By Henry C. Marble, M.D., F.A.C.S. 197 pages, illustrated. $7.00. Philadelphia and London: W. B. Saunders Co., 1960.

Theory of Shoulder Mechanism. By A. K. Saha, B.Sc., M.B., B.S., F.R.C.S.(Eng.), F.R.C.S.(Edin.), M.Ch. Orth.(L'Pool). 104 pages, 78 illustrations. $5.50. Springfield, Ill.: Charles C Thomas, 1961.

A Student's Guide to Obstetrics and Gynecology. By Christopher J. Dewhurst, M.B., F.R.C.S.(Ed.), M.R.C.O.G. 225 pages, 19 illustrations. $4.00. Philadelphia: J. B. Lippincott Co., 1961.

Current Therapy—1961. Edited by Howard F. Conn, M.D. 764 pages, no illustrations. $12.50. Philadelphia and London: W. B. Saunders Co., 1961.

Haematology and Blood Groups. Edited by D. A. G. Galton and K. L. G. Goldsmith. 169 pages, illustrated. $4.00. Chicago, Ill.: The University of Chicago Press, 1961.

The surgery of Mitral Stenosis. By Robert P. Glover, M.D., M.S. (Surg.), F.A.C.S., F.A.C.C., and Julio C. Davila, M.D., F.A.C.S., F.A.C.C. 195 pages, 41 illustrations. New York and London: Grune & Stratton, 1961.

Planning the Surgical Suite. By Warwick Smith. 456 pages, illustrated. $12.75. New York: F. W. Dodge Corp., 1960.

Pathogenesis and Treatment of Cerebrovascular Disease. Edited by William S. Fields. 556 pages, illustrated. $15.00. Springfield, Ill.: Charles C Thomas, 1961.

Traumatic Lesions of Peripheral Vessels. By Carl W. Hughes, M.D., and Warner F. Bowers, M.D., M.S., Ph.D. 191 pages, 58 illustrations. $8.00. Springfield, Ill.: Charles C Thomas, 1961.

The Conquest of Pain; Achievements of Modern Anaesthesia. By Ronald Woolmer, M.D. 240 pages, illustrated. $4.50. New York: Alfred A. Knopf, 1961.

Management of Fractures, Dislocations, and Sprains. By H. Earle Conwell, M.D., F.A.C.S., and Fred C. Reynolds, M.D. 7th ed. 1128 pages, 1227 illustrations. $27.00. St. Louis: The C. V. Mosby Co., 1961.

Surgical Diseases of the Lung. By Buford H. Burch, M.D., and Arthur C. Miller, M.D., F.A.C.S. 128 pages, illustrated. $8.50. Springfield, Ill.: Charles C Thomas, 1961.

Kranz Manual of Kinesiology. By Clem W. Thompson, Ph.D., F.A.C.S.M. 4th ed. 126 pages, 89 illustrations. $3.75. St. Louis: The C. V. Mosby Co., 1961.

Dunham's Premature Infants. By William A. Silverman, M.D. 3rd ed. 558 pages, illustrated. $15.00. New York: Paul B. Hoeber, Inc., 1961.

Atlas of Obstetric Technic. By J. Robert Wilson, M.D., M.S. 301 pages, illustrated. $14.50. St. Louis: The C. V. Mosby Co., 1961.

An Atlas of Pain Patterns; Sites and Behavior of Pain in Certain Common Diseases of the Upper Abdomen. By L. A. Smith, M.D., N. A. Christensen, M.D., N. O. Hanson, M.D., D. E. Ralston, M.D., R. W. P. Achor, M.D., K. G. Berge, M.D., G. W. Morrow, Jr., M.D., and A. H. Bulbulian, M.S., D.D.S., F.A.C.D. 54 pages, illustrated. $12.50. Springfield, Ill.: Charles C Thomas, 1961.

Clinical Neurosurgery. Proceedings of the Congress of Neurological Surgeons. Miami Beach, Florida, 1959. Vol. VII. 272 pages, illustrated. $12.00. Baltimore: The Williams & Wilkins Co., 1961.

Neoplastic Disease at Various Sites; Cancer of the Rectum. Edited by Cuthbert E. Dukes, O.B.E., M.D., M.Sc., F.R.C.S. Vol. III. 295 pages, 82 illustrations. $10.00. Baltimore: The Williams & Wilkins Co., 1960.

Surgery of the Esophagus. By Raymond W. Postlethwait, M.D., and Will Camp Sealy, M.D. 478 pages, 200 illustrations. $30.00. Springfield, Ill.: Charles C Thomas, 1961.

Cancer Progress 1960. Edited by Ronald W. Raven, O.B.E. (Mil.), T.D., F.R.C.S. 242 pages, 45 illustrations. $12.00. London: Butterworths, 1960.

Orthopaedia. By Nicolas Andry. Facsimile Reproduction of the First Edition in English, London, 1743. Vol. I, 230 pages, illustrated; and Vol. II, 310 pages, illustrated. $10.00. Philadelphia and Montreal: J. B. Lippincott Co., 1961.

Strangulation Obstruction. By Isidore Cohn, Jr., M.D., D.Sc. (Med.) 259 pages, 85 illustrations. $11.75. Springfield, Ill.: Charles C Thomas, 1961.

The Health of the Presidents. By Rudolph Marx, M.D. 368 pages, no illustrations. $5.95. New York: G. P. Putnam's Sons, 1960.

Management of Hypertensive Diseases. By Joseph C. Edwards, M.D., F.A.C.P., F.A.C.C. 420 pages, 68 illustrations. $15.00. St. Louis: The C. V. Mosby Co., 1960.

The Parenchyma of Law. By David W. Louisell, LL.B. and Harold Williams, M.D., LL.B. 482 pages, no illustrations. $12.50. Rochester, New York: Professional Medical Publications, 1960.